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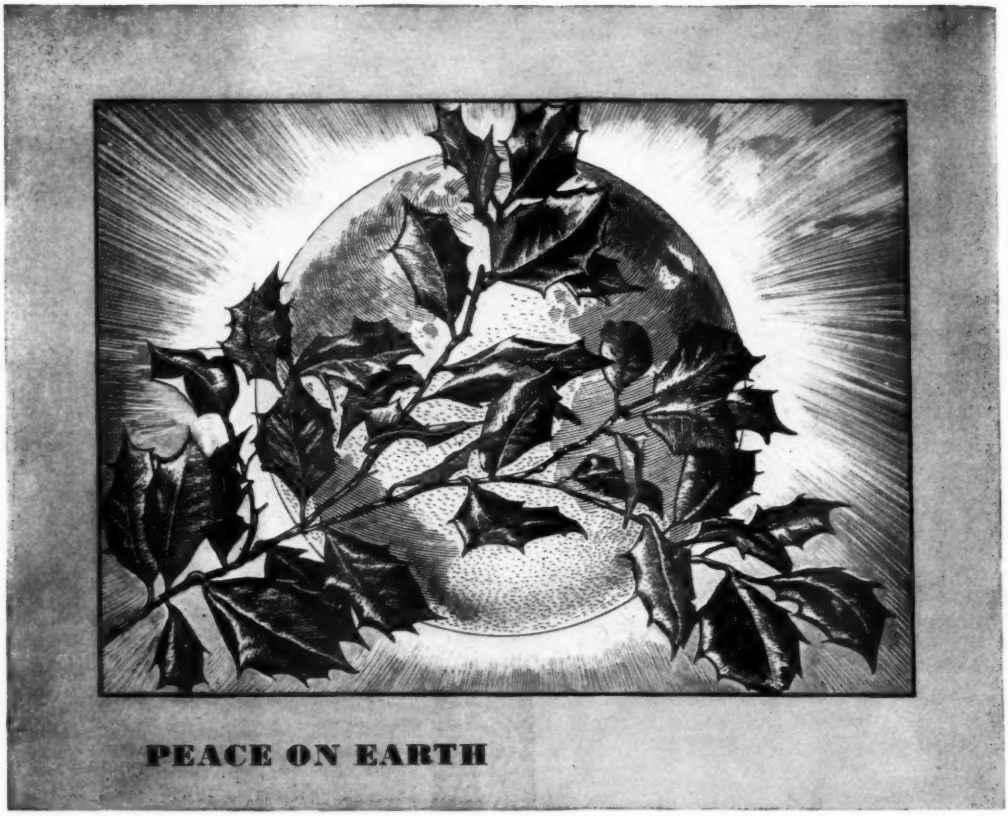

. . . TO MEN OF GOOD WILL

That all men everywhere may breathe again as free men ☆ ☆ That suffering and oppression may vanish forever from the earth ☆ ☆ That all men may regain their self-respect ☆ ☆ That the labor of all men may be devoted to the good of mankind ☆ ☆ That the pain and the hurt of all men be mercifully healed ☆ ☆ That all may live in peace forever!

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THE SIGNIFICANCE OF RHEUMATIC FEVER TO THE COMMUNITY

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RHEUMATIC fever continues to be one of the important diseases which remains unsolved in most of its public health aspects. It is one of the common diseases which affects the general public, and which occurs in all communities and all walks of life. It occurs most frequently in young people, although the effects on the heart may be crippling and last for years into adult life, or the after-effects on the heart may be recognized only in later years. During the past hundred years the disease has been more and more clearly differentiated from other forms of rheumatism and the special features seen in children were accurately described more than fifty years ago by the English physician, Cheadle. During this time the greatest interest of the medical profession has been centered chiefly on the after-effects on the heart and most of the emphasis has been placed on this phase of the disease, studying the nature of these after-effects, what might be done about them in the way of relieving the individual patients, and at times wondering what might be done about the initial onset of rheumatic fever. A great deal of effort has been spent by many workers to establish the cause of this infection, but little or no real progress has been made in this direction. It is generally believed that there is some relationship between rheumatic fever and streptococcal respiratory infections. It is agreed that the discovery of the etiology will be most important and that work must be continued in that direction. However, there are many other points which have been added to our basic knowledge and, in time, the application of this knowledge will be useful in reducing the extent and severity of the disease. Very little has been learned in the field of preventive medicine that can be of much use for the individual person who acquires rheumatic fever and, in this respect, we must continue to do the best we know, which is little more than what was known to, and practiced by, the earlier physicians. But in the field of public health, great advances have been made and much can be accomplished, provided certain measures can be carried out for the whole community which result in real protection for the individual. This same situation is equally true for several other important diseases; for example, tuberculosis and infantile paralysis in which, in each case, the cause of the disease and the way in which it is spread is now well known, but where no specific form of treatment exists with which the individual patient may be relieved.

Incidence.—It is difficult to determine whether the incidence of rheumatic fever is increasing or decreasing. More and more young people seem to be reporting with the disease, but the actual rate of increase is not easy to bring under accurate statistical analysis. The disease is not reportable in all communities; and such surveys as have been made are limited in scope, have

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been applied to specially-selected groups, and are indirect in the source of figures. Also, the public is more aware of the meaning and dangers of rheumatic fever and, no doubt, many children are reporting for examination and care. Physicians are more and more alert to recognize borderline cases, especially those occurring in early childhood and in sections of the country where, heretofore, the disease was thought to be infrequent. It seems evident now that in many large areas where the disease has a low incidence, many subclinical cases have not been recognized either because the symptoms were so mild that they could not be classed as rheumatic fever, or the disease had such a mild course that little or no effect on the heart resulted and the cases were missed. Whenever careful search has been made in those areas by workers familiar with the mild and protean symptoms, many more cases have been found before heart disease has resulted. Epidemiologic studies must differentiate between the attack rate for rheumatic fever and the incidence of heart disease. Again, studies have shown that a similar situation exists for infantile paralysis. The number of cases with permanent residual muscle paralysis is very low in comparison to the number of individuals who have demonstrable reactions indicating previous invasion by the virus endemically or during an epidemic. Improved school health services have uncovered many children with rheumatic fever who would otherwise be missed. All these factors, therefore, tend to increase the case and attack rate in any community. As far as we know, too, the secondary factors which enter into the etiology of the disease continue as before. Some are probably on the increase, together with several other new factors of this same class which have appeared and tend to increase the rate of incidence. Whether the disease is increasing is important, but the fact that more and more patients are coming in for care, and the load on medical facilities and community care and responsibility is increasing, places a greater responsibility on the medical profession and community agencies to care for these individuals with rheumatic fever.

Relation to Growth.—One characteristic of rheumatic fever has been the fact that initial attacks occur only in young people before complete biologic and physiologic maturity has been reached. The peak of incidence is during the semi-decade from 10 to 15 years with a rapid rise in rate before those years and a rapid fall after the same period. This is the period of life when the growth process is evolutionary and progressive. Other forms of arthritis are rare during this same time, and those that do occur are rarely associated with heart disease or other changes in body tissue similar to rheumatic fever. This is strongly suggestive that there may be some relation between rheumatic fever and the growth process. Either the sensitivity of body tissue to the streptococcus may be altered materially or the cell metabolism may be disturbed. Stroptococcal infection during other periods and during the same period in nonrheumatic subjects do not produce attacks of rheumatic fever. This same phenomenon may account for the confusion which has existed in respect to tuberculosis. For many years childhood tuberculosis has been confused with first infection types of tuberculosis. While it is true that the course of tuberculosis is strongly modified by the age of first infection, the first attack is generally similar at any age, making due allowance for the type of tissue in which the lesion occurs. The relationship of these and other diseases to the growth process is therefore of great pediatric importance and the subject is one for research examination.

Public Health Approach.—Probably the most important and hopeful trend at present is the shift of interest from the care of the person sick with rheumatic heart disease, with its crippling and often fatal effects, where it has been placed for so long, to the public health aspects of prevention of rheumatic fever in general. Especially important is the early recognition during childhood of first attacks of rheumatic fever long before the heart has been injured and even, in many instances, in changing the situation in a rheumatic family so that even first attacks may be prevented altogether. These public health aspects then result in the most effective form of preventive measures. It is still a medical problem to provide intelligent, constructive care for patients who have had rheumatic heart disease recently or still have old chronic crippling hearts with muscle and valve damage. These patients are numerous and many of them live for years fairly comfortably, but their efficiency is reduced and their care is an economic loss and liability. But if a community can manage to pro-

vide better socio-economic conditions for its citizens through improved housing and an opportunity for more healthful outdoor activities; less crowding and an intelligent consciousness of good nutrition; good public health control of communicable disease, particularly streptococcal respiratory colds and sore throats, with facilities for careful examination of children suspected of having rheumatic fever; then the rate will surely decrease substantially and effectively. This has been accomplished to a great degree in the case of tuberculosis control, and a more thorough application of these principles will reduce further the tuberculosis rate as well as the rheumatic fever rate.

Two factors may be described which have contributed in recent years to an increase in the rate of rheumatic fever. Both these factors continue in force and have become much more important. One is the migration of larger numbers of people from one community and one section of the country to another, particularly from the southern sections to the north (and in this case this has great importance to the negro race, for a long time considered more or less free of rheumatic fever), and from rural sparsely settled regions to the urban thickly settled centers where many of the secondary factors in the occurrence of rheumatic fever are poorly controlled and are prevalent. This has been due, of course, to the automobile and to changes in industrial employment. The second factor has been the war with all the changes in population centers incidental to this situation. In every instance the living conditions prevailing in many cities and industrial or war centers have become congested and in many cities have resulted in a lowering of facilities for housing, a shortage of [food supplies] especially essential foods, crowding in schools and various conditions taxing every public health facility to the utmost, and maybe resulting in lowering of adequate care in general. Individuals who are susceptible to the disease have moved into the areas in which the infection prevails and have promptly shown first attacks. These individuals have been not only members of the armed services in training centers but members of their families as well, and others centered in war industry areas.

Proposed Effective Control Measures.—What can be done to offset these trends and to control the disease? One can mention procedures and policies which should be considered and worked out.

1. A careful registry of known rheumatic subjects through reporting of cases with careful follow-up of these cases wherever they may go and as long as they remain active will give accurate information about the number of cases and their distribution. The purpose of this registry is not so much to serve as a case-finding method or to isolate such cases but to enable one to observe many points in the natural course of the disease where it exists. The opportunity to follow one patient from the onset of the disease into later adult life is not often possible, and yet this is most essential to a good understanding of what changes occur in patients who live and how they meet the strain of later life.

2. Adequate medical and professional care for children and young people during convalescence from respiratory infection, especially sore throats. A most effective method may be full medical examination when children report back to school or to work after being ill to see that the heart is normal, that no rheumatic symptoms are present, and that the nose and throat area is clear of infection.

3. Adequate periodic health examination of all people by physicians especially trained for this and who themselves are interested in this general phase of health, searching naturally for the common physical defects such as bad tonsils and teeth, but also for poor nutrition, poor posture, poor health habits and with an assessment of the child's growth and development, his socio-economic status and his probable susceptibility to all infections. This is not done at present in the usual health examination which is rarely more than a brief and often careless medical inspection. Unless the examination is done intelligently and constructively, its main purpose may be defeated.

4. Improvement of all phases of living conditions for people in lower economic levels by education of these individuals; by proper laws for better housing; by better food control and distribution; by establishing more and better opportunities for outdoor activities in parks and playgrounds and for easy transportation to suburban areas. It might be possible to have susceptible families change their residence to a more

favorable location in the country or in the south, either temporarily or permanently. This has been done in the army for soldiers with rheumatic fever with satisfactory results. These and other phases of this general idea come within the scope of community public health and planning. While rheumatic fever is not confined to people in low socio-economic levels, or to those who live in crowded cities, it is certainly much more frequent and severe there, and the most effective measures will be those directed at this low-privileged group. Modern knowledge of nutrition has shown that it is not so much the quantity of food, fresh air and exercise as the quality of these factors which may underlie the presence of this and other similar diseases. This means, therefore, not so much the expenditure of more money, public or private, but a more intelligent use of such funds as are already available. This is a most important viewpoint to have these days when great thought and effort is being given to the problems of providing better living conditions and health for the general population.

5. Adequate facilities must be provided for the medical care of rheumatic subjects. This should include properly-trained professional workers, such as doctors, nurses, social workers, nutritionists and others when and where rheumatic fever is prevalent. Many of these must have specialized training so they may serve in diagnostic centers. Facilities for the care of rheumatic children should include adequate supervision of the home so that attention can be given to contact children in the home, older occupants, food and sleeping, and all activities. The home situation in every instance should be appraised and evaluated in terms of what can be provided for the patient and his environment. The most important approach to the real problem of prevention of rheumatic fever is the reconstruction of living conditions in the home. Shifting of responsibility for medical care to outside institutions of any sort is at best a poor compromise in the ultimate solution of the patient's recovery. Temporary foster-homes may be arranged for the care of patients at low cost under the careful direction of recognized child-placement agencies subject to proper regulation by state and local authorities, and where foster mothers have been specially trained to care for rheumatic children and understand the problems involved such as regular health habits, directed and adequate exercise, extra rest, quiet stable emotional environment, good simple food, and education. In general, adequate beds for the care of rheumatic subjects are available in established hospitals and clinics, but there is a lack of adequately-trained personnel to manage the wards and clinics, and especially there is a lack of adequate beds in convalescent sanatorial homes and hospitals such as are available for patients with tuberculosis. There is considerable evidence to show that rheumatic subjects need not be kept in bed for such long periods. Improved methods for determining activity of rheumatic infection makes it possible to recognize accurately the termination of the period for bed rest. In this way many patients may be returned to normal physical activity sooner and with less risk. Many rheumatic children have been kept in bed for too long (to their own detriment), and are occupying space which should be available to others. There has been a tendency to use beds both in hospitals and convalescent sanatoria for patients with advanced heart disease rather than to reserve such space for the early and probably preventable stage of rheumatic fever. There are many rheumatic subjects who become severly and acutely ill who are in need of hospital beds for intensive medical care and diagnosis who can safely return to their homes after short periods. But if these beds are occupied by the chronically ill who are confined for long periods, then the turnover is very slow and the total number of patients who receive essential care is lowered.

6. Careful study is needed to rehabilitate patients who have recovered from attacks so they may be directed to useful lives and to earning a good living. This rehabilitation should start during the convalescent period after attacks, should continue through the vocational training period and be projected into the employment period. At each medical examination the patient's fitness to do his job should be given careful consideration so that adjustments and changes can be made in time. Patients must be instructed in what their future may be; what their physical limitation may be; where they may live to the best advantage; and what sort of work they are best suited for. This implies many phases and involves many agencies with the coöperation of educators, physicians, employment agencies, train-

ing centers, and industrial management. Life insurance authorities are also vitally concerned in the direction of the patients into the proper levels of activity for it can be shown that morbidity and mortality rates are substantially lowered by careful attention to these factors. Industrial health authorities can be shown that rheumatic subjects are able to produce good work without handicap and compensation when the rheumatic individual is properly adjusted to his job and environment. This is a most important conception now when many servicemen will be returning to jobs after having had rheumatic fever during their military period. These men must be restored to jobs suited for their capacity for work and this can be done effectively.

Two other medical procedures may be included for discussion which are of public health interest in the control of rheumatic fever. One of these is the relation of the incidence of rheumatic fever to bad tonsils; whether the individual case is influenced by removal of tonsils; and whether the community rate can be lowered by removal of tonsils in all children. It can be stated that rheumatic fever attacks occur whether tonsils are in or out, and that having good tonsils or no tonsils is no guaranty of freedom from rheumatic fever. It is also true that rheumatic individuals are improved when bad tonsils are removed. Whether this is directly an effect on the incidence of respiratory infections and a lowering of the subsequent rheumatic attack rate, or an indirect effect resulting from the general improvement in the child, both locally in the nose and throat with improved breathing and ventilation with greater freedom from colds, and from removal of a load of infection, is not always clear. Undoubtedly a chronically infected tonsil like any other focus of infection with recurring periods of activity, will sensitize the individual to the infection so that attacks of rheumatic fever follow one or another acute phase. One other very important phase of the problem of prevention of attacks is for the examining physician to be thoroughly familiar with the condition of the nose and throat area so that as cases are followed any change can be recognized and treatment started. This requires careful medical inspection of the area at each visit, bacteriologic cultures if necessary, examination by a nose and throat specialist in consultation, and other special techniques when the occasion arises. The nose and throat area must be put in good order and kept so at all times. The tonsils are only one part of this area and their importance as the location of the infection has been overemphasized. It may be true that infected tonsils are only the end-result of a more general infection in the nose and throat. Infection in other areas of the body may at times give rise to attacks of rheumatic fever but the principal and usual sensitizing focus is the nose and throat area. These measures are directed toward preventing and managing phase I of a rheumatic episode.

The other procedure for discussion in this same category is the use of sulfonamide drugs for control of recurring respiratory infection in rheumatic individuals. It has been shown that small doses of such drugs can be given daily (month after month) to rheumatic patients without harm, and that the number of colds and respiratory infections can be greatly reduced if not prevented. If the sensitizing attack of phase I can be prevented, then these patients do not have Phase III of rheumatic fever. Small doses of the drug are required, but it must be taken continuously and regularly during the winter season or through the whole year. Close medical supervision is necessary and, at least at present, it is not a safe procedure to give the drug to patients unless this supervision is guaranteed. Furthermore, the question will arise of using the drug in the same way for all members of the family where the rheumatic patient is housed in order to control contact infections, and further reduce the load of sensitizing infections. This procedure would be not unlike a public health attempt to control malarial infestation in a community by the administration of quinine to all inhabitants in addition to mosquito control, housing, screening, et cetera. It is also not now unreasonable to conceive of using sulfonamide drugs in the same way to control streptococcal infections in the total population.

There are three secondary phases of the problem of rheumatic fever related to the etiology of the disease which remain unsolved. One of these is the question of heredity. Susceptibility to a given disease as an inherited characteristic may be difficult to establish, and careful study through several generations in large groups is necessary. Genetic studies by May Wilson indicate definitely that there are families with more cases of rheumatic fever, living under conditions compara-

ble to other families with no cases. The high incidence rate is not explainable entirely on the basis of contact infection, and her conclusions are that there is some significant inherited genetic characteristic. In this same connection the question to constitutional type, race, et cetera, may be mentioned. At present very little is known about constitutional type in relation to any disease. But this subject is not easily examined, and the future may reveal some factor present in an individual or a group which prediposes of rheumatic fever or other conditions. Some such factor would seem to be necessary to explain the spotted incidence in any areas. This unknown factor might be readily transmissible from parent to offspring. The likelihood even now is great enough to warn rheumatic subjects not to intermarry. It can be stated that there is no fixed racial immunity or predisposition to rheumatic fever.

A second phase in the etiology of rheumatic fever which needs investigation is the relation to climate. The disease is more frequent in the north temperate zones, and in the larger urban industrial centers where crowding, long winters, cold changeable weather, and other unfavorable climatic factors exist. In recent years the high incidence rate of rheumatic fever in the Rocky Mountain states has called for further explanation, for many of these cases occur under conditions which are in no way similar to those in the New England states. Whether this is due to altitude, to lack of sunshine, or to some other climatic factor is not known. This may be the factor which could account for cases in isolated rural areas far removed from congested cities and frequent exposures to respiratory infections. It has been suggested that a high diurnal variation in temperature may be responsible. The older idea of dampness alone, and basement living as an etiologic factor does not seem true.

The third phase in the possible etiology of the disease is that the attack of rheumatic fever is a form of hypersensitivity to streptococcal infections similar in general to other forms of allergy. This idea has been suggested for a long time and has been discussed freely. There are many clinical features of the disease which justify the assumption and the idea is sound. Recurring respiratory infections in early childhood may sensitize susceptible individuals during succeeding years until under some set of circumstances, another infection called phase I may be followed through a silent phase II period into a period of rheumatic activity called phase III. This pattern of behaviour is so constant that many workers are willing to accept this general conception. Many and maybe all the morphologic tissue changes occuring in the body, including the heart, can also be explained on this basis. Many of the phenomena associated with attacks, including bacteriologic studies of cultures as well as seriologic reactions, also suggests that this is true. Allergy is a new conception of the expression of the body response to disease, and many points are not yet explained or understood, but there is promise that the future will bring a correct answer.

Two recent developments in the public health aspects of the disease should be mentioned. One, the United States Government through legislative acts of Congress has authorized grants-in-aid to rheumatic children in states through the program of services for crippled children. These programs are carried on by state and local agencies administered under the jurisdiction of the Department of Labor through the Children's Bureau as a part of the Social Security Act. The purpose of these programs is to offer aid of all types in selected areas to children who are unable to secure special medical care for lack of funds. The programs are essentially medical service to the individual but, indirectly, they are important forms of preventive medicine, and they should be valuable steps toward the control of rheumatic fever. These programs have been in operation only a few years and because of lack of sufficient funds are restricted to small areas in each of about twenty states. Undoubtedly, much will be learned from studies being carried on under these plans. Second, several interested groups have organized a Council on Rheumatic Fever under the general supervision of the American Heart Association. The constituent groups represent the medical profession, public health nurses, sociologists, and others who have a professional interest in the control of this disease. This council will be formed in a way similar to other health and medical councils, so that some coördination may be given to all the interests concerned, educational, vocational, medical, research, and otherwise. The organization of this council has been started only this year but considerable progress has been made.

A CONSIDERATION OF THE PHYSIOLOGIC ACTION OF THIO-URACIL AND OTHER GOITROGENS

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THE observation that thio-urea and certain of the sulfonamide compounds induce in experimental animals a marked hyperplasia of the thyroid gland[1,2,7] has afforded a new impetus to the study of the physiology of this important endocrine gland.

A decade or more ago, students of the function of the thyroid produced in animals extreme hyperplasia of the gland by feeding the leaves of cabbage or other members of the Brassica[6,9,15,16] family. Cyanides were subsequently found to be goitrogenic.[10] Likewise soybean flour, when added to diets of experimental animals, induced enlargement of the thyroid.[14] Phenylthiocarbamide produced large hyperplastic goiters.[12] All of these substances interfered in some way with the metabolism of iodine and the thyroid response occurred as a result of lack of iodine. If iodine was provided in adequate amounts during the time these substances were given to the animals, goiters were not produced.

During the past two years it has been shown experimentally that there are two rather clearly defined groups of chemicals which appear to depress thyroid function and, as a result, induce extreme hyperplasia of the thyroid together with lowered basal metabolic rates. One of these groups includes thio-urea and its derivatives, which are sulfocarbamides in which the oxygen of urea is replaced by sulfur; the other group of chemicals which depress thyroid function contains members of the aniline series. These drugs, when given to animals either by mouth, as in purified diets or in their drinking water, or parenterally by injection, induce very rapid changes of thyroid function, which result in increased heights of the acinar cells of the thyroid and in extreme cellular hyperplasia (Figs. 1, 2, 3 and 4).

In contrast to the fact that iodine when coadministered with the goitrogen will prevent the development of cyanide goiters, repeated experiment has shown that iodine, even in exceedingly large amounts, will not prevent the thyroid changes which these newer goitrogens induce (Fig. 5). On the other hand, the thyroid hormone, thyroxine or desiccated thyroid gland not only will prevent the development of a goiter but will restore normal histologic patterns in the thyroids after the goiters have been produced and while the drug is still being administered (Fig. 6). This relationship of the thyroid hormone to the failure of these newer goitrogens to induce thyroid hyperplasia was the basis of the opinion suggested by Astwood[2] and others that these thyroid depressants act in some way upon the mechanism in the enzyme system which functions in the conversion of diiodotyrosine to thyroxine.

Recently my colleagues and I have learned in our laboratory that the sulfone, promizole (4,2'-diaminodiphenyl-5'-thiazolesulfone), likewise has goitrogenic potencies.[5] The administration of 5 mg. per day, either by mouth or parenterally, to a growing immature rat produced within a week or ten days a degree of thyroid enlargement not unlike that which appears when thio-uracil, at a level of 0.1 per cent is provided rats in their drinking water.

When either of the goitrogens (thio-uracil or promizole) was given to young rats in the amounts stated, changes in their thyroid glands were detected within twenty-four hours. The colloid of the acini, which normally stains a reddish pink with acid dyes, was poorly stained and presented a stippled, punctate appearance, rather than the clear homogeneous pattern normally seen. The colloid retracted from the acinar cell membrane and gradually contracted into small, amorphous fibrous nodules. In ten days to two weeks, all traces of colloid had completely disappeared from the gland.

While these changes occurred in the colloid and within forty-eight to seventy-two hours of the onset of the administration of the goitrogen, an increase of the height of the acinar cell was observed. This was the first sign of hypertrophy. Thyroid cells increased rapidly in height and in number, and papillary projections protruded into the lumina of the acini. The size of the lu-

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Fig. 1. Anterior view *(left)* and posterior view *(right)* of a portion of the trachea and larynx of a normal rat, showing the thyroid attached.

Fig. 2. Anterior view *(left)* and posterior view *(right)* of a portion of the trachea and larynx of a rat which has received thio-uracil in its drinking water for a period of five months.

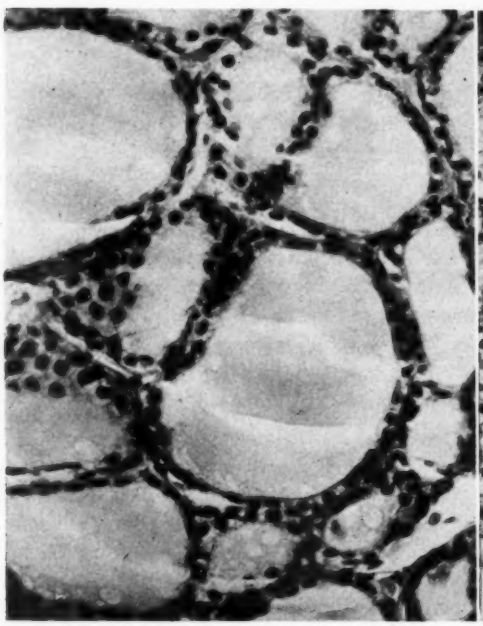

Fig. 3. Section of the normal thyroid gland, showing the character of the colloid and the epithelium in the unstimulated gland.

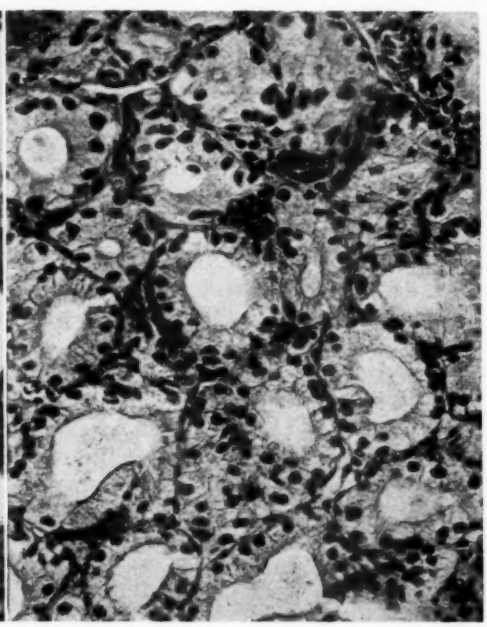

Fig. 4. Section of the thyroid gland of the animal which had received thio-uracil, shown in Figure 2.

mina correspondingly decreased and gradually the extent of hyperplasia and the encroachment of the thyroid epithelium practically abolished all spaces previously occupied by the colloid substance. New acini arose within the hyperplastic wall of the older acini, as a result of a separation and a rearrangement of preëxisting cells into new units. These new acini subsequently increased in size and as a result of all of these rapid changes within the gland a goiter of greatly increased weight, composed of a greatly increased number of acini, was formed.

The manner in which these goitrogens depressed thyroid function has been extensively studied in recent months but the mechanism is incompletely understood. Rawson, Tannheimer and Peacock[11] have recently classified goitrogens into iodine-resistant and iodine-inhibited goitro-

gens. Potassium thiocyanate, for example, is an iodine-inhibited goitrogen, for its administration to an animal did not produce a goiter when iodine was coadministered with the drug. Thio-urea, thio-uracil, promizole and sulfaguanidine, on the other hand, are iodine-resistant goitrogens, for even large amounts of iodine when coadministered with these drugs will not inhibit the formation of the goiter.

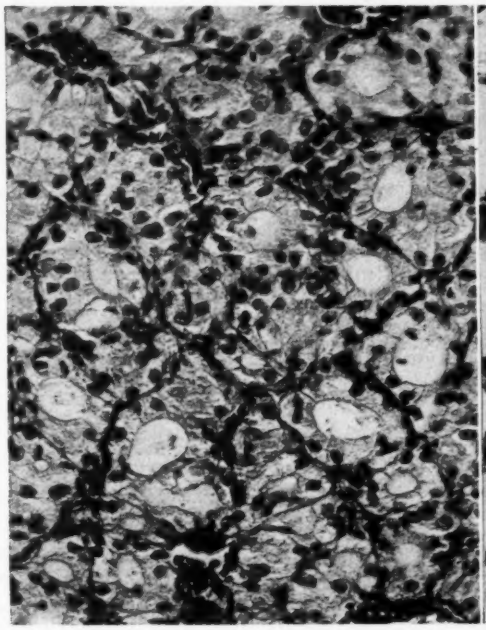

Fig. 5. Section of the thyroid gland of an animal which had received thio-uracil for five months and then was given 500 micrograms of iodine, as sodium iodide daily for fourteen days. The histologic pattern remained unaffected by iodine.

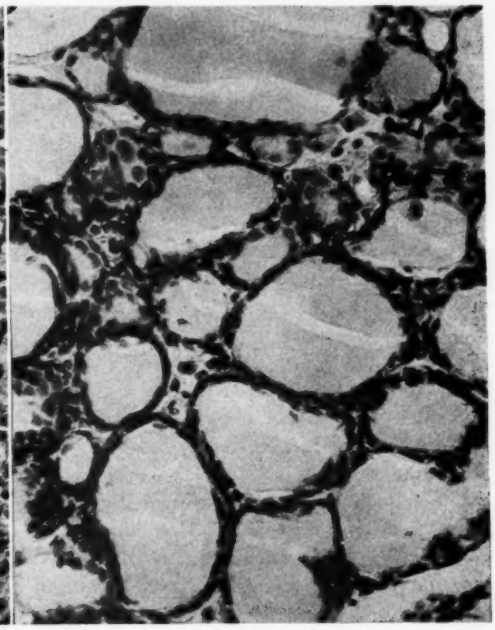

Fig. 6. Section of the thyroid gland of an animal which had received thio-uracil for five months and then was given 50 micrograms of thyroxine daily for fourteen days. The histologic pattern was essentially normal.

These investigators have shown that goiters produced by these two types of goitrogens react differently to injected iodine when radioactive iodine, I^{131} is administered. Four hours after radioactive iodine had been given intraperitoneally to white rats, an average of 56 per cent of the injected iodine had been taken up by the thyroids of normal animals serving as controls. Thyroids previously made goitrous by administration of potassium thiocyanate collected an average of 86.5 per cent of the iodine administered, while the thyroids of rats made goitrous by administration of thio-uracil collected in the same period only 10.1 per cent of the iodine injected. The goitrogen, thio-uracil, thus in some way appears to prevent the collection of iodine by the thyroid cells.

Iodine concentrations in the thyroid gland are considered to reflect the amounts of active thyroid principle which is present in the thyroid at any one time. Astwood and Bissell[3] have recently reported their study of the iodine content of the thyroid glands of young rats which were given thio-uracil in their drinking water at the level of 0.1 per cent. They detected a significant decrease of the amount of iodine in the thyroid within twenty-four hours after the drug had been given to the animal. Within five days, the thyroid iodine level had dropped to as low as one-thirtieth of the normal iodine content of the thyroid. When the drug was withdrawn and pure water for drinking restored to the animals, the iodine content of the thyroids increased rapidly to normal levels. Thus these studies of Rawson and of Astwood and their collaborators clearly show that the thyroids of animals given thio-uracil not only fail to take up iodine from the blood stream but rapidly decrease their own iodine stores of the colloid and as a result prob-

ably fail to elaborate the thyroid hormone, thyroxine.

Also using labeled iodine (inorganic iodine, I^{131}) as a test object, Franklin, Lerner and Chaikoff[4] have studied the influence of the goitrogen thio-uracil on the formation of thyroxine and diiodotyrosine by the intact thyroid gland. Rats were given the drug at a level of 0.035 per cent in their diet for seven days. Each animal thus received from 3.4 to 4.2 mg. of thio-uracil per day. When administration of the drug was stopped after seven days of treatment, radioactive inorganic iodide was injected into the animal. Forty-eight hours later the thyroid glands of these animals were analyzed for their total radioactive iodine, for radiothyroxine and for radio-diiodotyrosine. The results of Franklin, Lerner and Chaikoff confirm the conclusions of other studies of the depressed functions of such thyroids and show that the capacity of the goitrous gland to pick up and incorporate injected radioactive iodine into diiodotyrosine and into thyroxine is greatly retarded.

Basal metabolic rates of experimental animals invariably fell whenever these thyroid depressing goitrogens were administered. This was true whether the goitrogen was a nitrile, as potassium thiocyanate, or whether thio-uracil or sulfaguanidine was given. MacKenzie and MacKenzie[5] have recently reported that a fall in the basal metabolic rate of 10 per cent occurred in five to seven days of treatment with sulfaguanidine. This fall increased to 20 per cent in ten to fourteen days and appeared to coincide with the depletion of colloid from the thyroid acini. These decreases in rates of oxygen consumption were likewise not inhibited by giving iodine but they were entirely prevented by the daily administration of 1 microgram of thyroxine per 10 gm. of body weight. The mechanism of inhibition was entirely reversible, for the withdrawal of the sulfaguanidine from the diet resulted in a prompt rise of the metabolic rates of these animals.

Although the mechanism of the action of these iodine-resistant goitrogens is not clearly understood, their administration appears to prevent the iodination of tyrosine and the subsequent formation of thyroxine. The resulting hyperplasia of the thyroid is evidently mediated through the pituitary gland, for both MacKenzie and MacKenzie and Astwood and his associates have shown that, when goitrogens were given to animals whose pituitary glands had been removed, hyperplasia of the thyroid did not occur. Furthermore, it has been stated that the cells of the pituitary in animals which were made goitrous by these thyroid depressants resembled those of animals which had been previously thyroidectomized.

Rapid changes of the pituitary gland of experimental animals follow thyroidectomy. These include a marked loss of the acidophils, accompanied by an increase of the number of vacuolated basophilic cells derived from the chromophobes. These changes are thought to be regressive and resemble similar changes which ensue upon castration. These vacuolated basophils are the "thyroidectomy cells" described in the literature. The increase of the size of the pituitary gland in animals which have received the goitrogen for prolonged periods, as well as the presence of the large vacuolated basophilic cells, is a reaction identical with pituitary changes which follow thyroidectomy.

A very fine balance is thought to exist between the functions of the pituitary and those of the thyroid gland. Salter[13] has designated this relationship "the pituitary-thyroid axis" the balance of which may be maintained by the levels of thyroxine and of thyrotropic hormone circulating in the blood stream. It would seem that this balance between the thyroid and pituitary functions must be seriously modified by these goitrogens. Although there are as yet no experimental data to sustain the conviction that the level of thyroxine in the blood of an animal is lowered after one of these goitrogens has been given, yet, it is quite probably true. The loss of thyroid iodine and the failure of the thyroid to take up iodine and to convert it into thyroxine are established facts which suggest that the blood level of the thyroid hormone is reduced.

If the concept of Salter is correct, then it is reasonable to conclude that the changes observed in the pituitaries of animals that have hyperplastic thyroids may be due to some stimulus exerted upon the pituitary by the lowered thyroxine level in the blood stream. This may result, then, in an increase of the elaboration of the thyrotropic hormone by the pituitary, which in turn stimulates the thyroid epithelium, resulting in the hyperplastic changes observed in the gland. There are no published data on the bio-assay of

thyrotropic hormone in the pituitaries of goitrous rats but preliminary studies in this laboratory on the effect upon the acinar cell heights of thyroids of day-old chicks have led my colleagues and me to conclude that the amounts of thyroid-stimulating hormone elaborated by the pituitaries of goitrous rats may be greater than normal.

Summary

Thio-urea and its derivative thio-uracil, many sulfonamide compounds, notably sulfaguanidine, and at least one sulfone, promizole, are goitrogens which, when administered to experimental animals, induce marked hyperplasia of the thyroid gland and lower basal metabolic rates. The effect of these drugs is reversible. Normal histologic patterns were restored and basal metabolic rates were elevated rapidly upon cessation of administration of any of these drugs.

Although the mechanism of action is not understood, these thyroid depressants apparently secure their effect by inhibiting the formation of thyroxine by the thyroid gland. Not only are thyroids subjected to the influence of these drugs unable to take up from the blood stream the required amounts of iodine, but they rapidly lose their normal iodine content. Thus at least one inhibitory influence of these goitrogens is to restrict the iodination of the thyroglobulin molecule, thereby restricting the amounts of thyroxine produced.

The coadministration of either thyroxine or desiccated thyroid with the goitrogen nullified its thyroid-depressing effect but even large amounts of iodine proved ineffective in preventing the thyroid changes. Thus, all data at hand favor the hypothesis that these goitrogens do not destroy thyroxine nor do they in any way lessen the needs of the organism for the thyroid hormone. Rather, they seem to inhibit the formation of thyroxine by preventing its synthesis in the thyroid cell.

Changes in the cells of the pituitary gland accompanied the prolonged administration of the goitrogen. These changes included an increase of the size of the anterior lobe and the appearance of numbers of basophils, presenting vacuolar changes. These cells are said to resemble the pituitary basophils which appear in animals made hypothyroid by thyroidectomy. Thus, the hypothyroid state induced by the goitrogen is somewhat like that which follows the removal of the thyroid. The increased size of the thyroid gland may be considered to be the result of the stimulus incited by increments of thyroid-stimulating hormone put out by the anterior lobe of the pituitary responding to low levels of the thyroid hormone in the circulating blood.

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THIO-URACIL THERAPY IN HYPERTHYROIDISM

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IN MAY of 1934, E. B. Astwood of Boston[1] published a report on the reduction of basal metabolic rate and the abolition of signs and symptoms of hyperthyroidism in three patients using thio-urea and thio-uracil by mouth. Since that time over 200 individuals with hyperthyroidism treated with thio-uracil have been reported in the literature. The purpose of this paper is to review the clinical experience to date, using illustrative case material from our own series and following this with a discussion of the merits and otherwise of this new form of therapy.

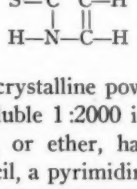
Fundamental considerations are in large part not discussed, being dealt with comprehensively by Dr. Higgins in another paper in this issue. However, to give due recognition to the original workers a certain amount of repetition will perhaps be excused.

In 1941, MacKenzie, MacKenzie and McCollum[16] reported a remarkable enlargement of the thyroid in animals which had been fed sulfaguanidine. In that year and in 1942 there appeared several papers[13,27,28] which can now be seen as contributory; but it was two simultaneously published studies by MacKenzie and MacKenzie[15] and Astwood, Sullivan, Bissell and Tyslowitz[5] which made clear the unique nature of the new goitrogenic agents of which sulfaguanidine is the prototype and thio-uracil the most recent example.

The goiters produced by these agents, unlike those produced by the older goitrogens[14,17,18,24,31,34,35,36], viz. soy beans, thiocyanate, cabbage, and seeds of the Brassica family generally, cannot be prevented or abolished by iodine administration. To make a long story short the currently accepted view[5,15,23,37] of the action of thio-uracil, as characteristic of the new thyroid drugs, is that it inhibits the uptake of iodine and the formation of thyroid hormone by the thyroid gland[4,7,8,9,23,25], colloid typically being reduced or depleted[5,11,15] and basal metabolic rate falling.[5,15] In the absence of normal thyroid function the pituitary is believed to overact, producing hyperemia and epithelial hyperplasia of the thyroid; this explanation of the thyroid hyperplasia is based upon: (1) the known action of the thyrotropic hormone of the pituitary, (2) observable histologic changes in the pituitary following sulfaguanidine administration, (3) the ability of administered thyroxin to prevent or abolish thio-uracil-induced hyperplasia of the thyroid, (4) the absence of thyroid hyperplasia in hypophysectomized animals given the new goitrogens.[5,11,15] The acceptance of this view is strengthened by a consideration of alternate explanations. General toxic effect is ruled out because some of the toxic agents are least effective and the effective agents do not significantly interfere with growth and development if thyroid is fed. Since parenteral is as effective as oral administration, inhibited formation of some essential metabolite in the gastro-intestinal tract does not appear likely. Elevation of tissue requirements for thyroxin or destruction of it is contradicted by the fact that administered thyroxin is normally effective despite the drug.[15]

Nature, Distribution, and Dosage of Thio-uracil

Thio-uracil (more properly, 2-thio-uracil) has the formula:



It[37] is a white crystalline powder, readily soluble in NaOH, soluble 1:2000 in water, insoluble in acids, alcohol, or ether, has no odor but a bitter taste. Uracil, a pyrimidine, is a constituent of plant nucleic acid. Thio-uracil emerged as the compound of choice, i.e. high effectiveness with low toxicity, after Astwood[2] had tested 106 compounds. In animals, sulfapyridine, sulfadiazine, sulfamethyldiazine, share with sulfaguanidine in being markedly goitrogenic; sulfathiazole and sulfanilamide are less effective. Thio-urea and other substituted ureas were also found to be active. In passing it is interesting to note that whereas there have been reports[24] of goiter induced in hypertensives by thiocyanate, so far no one has recorded such an effect for clinically administered sulfonamide. Thio-uracil is rapidly absorbed, the

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maximum blood level from a single small dose being reached in fifteen minutes. One-third of the usual dosage is excreted in the urine[37]; none has been found in the feces. Thio-uracil in the blood is chiefly in the cells, particularly the white cells. Other tissues which acquire the greatest concentration are the pituitary, thyroid, adrenal and bone marrow, the last organ being particularly worthy of note in respect to the toxic manifestations so far encountered.

Although higher dosages were originally used, the currently recommended scheme of administration[38] is 0.6 gms. daily (0.2 gms. t.i.d.) initially with reduction to 0.4 (0.2 b.i.d.) daily after two weeks or when definite clinical improvement occurs; after a further two weeks or on return of the basal metabolic rate or clinical condition to normal, the dose is reduced to 0.2 gms. (0.1 gm. b.i.d.) daily. Thio-uracil is available* as 0.1 gm. tablets which are taken orally. Maintenance dosage is generally 0.1 to 0.2 gms. daily. Some qualification about dosage in exceptional cases will receive later comment. Determination of blood levels of thio-uracil is no longer considered necessary.[38]

Results

The most extensive clinical experience with thio-uracil so far recorded has been that of Williams and Bissell[37] and Williams and Clute.[38] Present purposes will be well served by first sketching some of their principal findings. In all, these authors have recorded treatment with thiouracil of seventy-two patients with thyrotoxicosis including classic Graves' disease and toxic nodular goiter. No differentiation in results is recorded for the different types. It is important to note that almost all of their patients were ambulatory and performing their usual duties.

Fifty-nine of their seventy-two patients had either not received iodine at any time or for at least one month before treatment with thio-uracil. For the sixteen patients in this group with the highest initial basal metabolic rate (+55 to +89), the basal metabolic rate after four weeks of treatment averaged + 12 (range —8 to + 32); in six weeks the average basal metabolic rate of these was 0 (—15 to +15) and there had been an average weight gain of seven pounds. In general the metabolic rate of these sixteen patients was within the normal range in five weeks. For further noniodine-treated patients who were less toxic than the above, the decrease of basal metabolic rate to normal occurred more rapidly, the average time being three weeks in those whose initial metabolic rates were under +35. None of these individuals resisted thio-uracil therapy and the extreme time for return to normal metabolic rate was seven weeks. For the sake of brevity the general condition of patients is indicated by the basal metabolic rate because in the great majority of cases change in clinical status was in as good accord with the basal metabolic rate as is usually observed. Weight gain as an index of improvement was most marked during the fourth to eighth week of treatment. The similarity of the remissions to those following thyroidectomy had been carefully recorded[32,38], in respect of symptoms, weight, pulse, blood pressure, metabolism of calcium, phosphorus, nitrogen, creatine, and blood cholesterol. On the other hand there are certain unusual features associated with thio-uracil remission, at least in certain cases, and these will be discussed below in commenting upon our own cases.

A further thirteen of their seventy-two cases had received iodine within one month prior to thio-uracil therapy. The metabolic response was notably slower, normal values not being achieved until the sixth to eighth week. Gain in weight although eventually good was not as prompt as in the cases without iodine. Previous treatment with iodine therefore is seen to produce resistance or delayed response.

On the basis of their experience with all of the seventy-two patients, Williams and Clute remarked, "that this drug can be depended on in essentially all cases to lower the basal metabolic rate to a normal range and to maintain it at that level so long as treatment is continued. Associated with this response in the basal metabolic rate is a clinical remission of the disease with disappearance of tachycardia, hyperidrosis, nervousness, diarrhea, weight loss and other toxic manifestations." This then represents the favorable aspect of thio-uracil therapy. Untoward reactions, however, were not absent in their cases and will be reported along with the experience of others in discussing illustrative cases from our own experience.

*We are indebted to Dr. Benjamin W. Carey, Lederle Laboratories, Pearl River, New York, for the supply of thiouracil (Deracil) used in this study.

University of Minnesota Hospital Cases

We have had experience with twenty-six cases. Although there have been many distinctly favorable results, the group contains more unfavorable reactions than any series so far recorded. This may or may not be due to the prior selection that takes place in cases referred to this clinic; in any case those we have seen have had a high incidence of iodine-fastness and other complications. The cases have been under the direct management of the staff members responsible for the different services of Medicine and Pediatrics. The nature of the study has therefore to a certain advantage been that of a practical trial rather than a uniformly conducted experimental series. Bed rest, high caloric diet, supplementary vitamins and sedation have been used as they would have been if thio-uracil had not been employed. In general, rather than waiting for complete remission the cases have been subjected to thyroidectomy when the clinical condition warranted it.

Reduction of Signs and Symptoms of Hyperthyroidism.—For the purpose of evaluating disadvantages all cases are considered. However, in assessing the ability of thio-uracil to reduce metabolic rate and alleviate hyperthyroid signs and symptoms, seven cases in which thio-uracil was used too briefly for proper evaluations are excluded; in three of these, toxic reactions necessitated stopping the drug; the other four without any untoward reaction to thio-uracil were changed over to idodine and/or subjected to thyroidectomy at the discretion of the clinician in charge of the case. Of the remaining nineteen individuals, eight had not received preceding treatment with iodine. On the average these eight patients had an initial basal metabolic rate of +43 which in twenty-four days of treatment was reduced to +14, with a weight gain of five pounds and a reduction of 24 in the pulse rate. The eleven patients who had received iodine within one month of the time of starting thio-uracil had on the average an initial basal metabolic rate of +57 which was reduced in thirty-five days to +23 with corresponding gain in weight and reduction of pulse rate. These results agree with those obtained by Williams and Clute[38] and others[6,21,23,32,33], the iodine-treated patients again giving a slow response.

Illustrative cases are found in the following reports:

Case 19.—Good response; no iodine.

This forty-nine-year-old woman presented with symptoms of weakness, easy fatiguability, nervousness, irritability, palpitation, tachycardia, heat intolerance, dyspnea on exertion, increased appetite, and weight loss. She had had three attacks of similar symptoms in the past thirty years, relieved by prolonged administration of Lugol's solution. There had been no iodine medication for at least six months prior to her admission. Sedatives had been given without relief. On physical examination the blood pressure was 146/76, pulse 100-120. She was mildly hyperactive. Her skin was moist and warm. There was slight thyroid enlargement more noticeable on the left but no bruit. Marked quadriceps weakness, fine tremor, thinning and softening of the finger nails were noticed. There were no eye signs. The heart was normal in size and negative except for increased action and a systolic murmur. In view of the necessity of watching the white cell count in thio-uracil therapy it is interesting to note that her white count on admission was 3,800 with 39 per cent neutrophils. Blood cholesterol was 137 mg. per cent. Four satisfactory basal metabolic rate determinations established her initial rate at +61 per cent. She was started on 0.6 gm. of thio-uracil daily. At the end of thirty-one days the basal metabolic rate was +14 and the pulse rate was 70-74. There was a striking improvement in symptoms consistent with the change in pulse and metabolic rate; the patient had gained six pounds by the time of thyroidectomy which was undertaken on the thirty-ninth day of thio-uracil therapy, it being delayed until that time on account of the operative schedule. The operation and postoperative period were without incident. The 45 gms. of thyroid tissue removed showed a marked variation in colloid content and in the height of the epithelium.

The above case does not represent the best result in the group of ten noniodine-treated patients. Two other patients of equal severity had as good responses in twelve and twenty-seven days, respectively. Still four others with initially moderate hyperthyroidism were successfully prepared, two for thyroidectomy and two for chronic maintenance, in seventeen, twenty-two, eighteen, and twenty days. The three remaining cases were definitely less successful than the example given; in two of these, toxic reactions occurred and the drug was stopped. The third with an initial basal metabolic rate of +51, received thio-uracil for twenty-six days, at the end of which time the basal metabolic rate was +35 and the weight gain six pounds. There was, however, no drop in pulse rate and the subjective response was poor. The thio-uracil was stopped and Lugol's solution substituted. After eight days the basal metabolic rate was +8 per cent with some subjective improvement. A successful thyroidectomy was

performed. This then gives a brief picture of the patients not receiving iodine. The toxic manifestations remain to be discussed but one further point should be made. The case example given represents what approximately may be expected, i.e., remission to normal basal metabolic rate in approximately four to five weeks. The length of this waiting period deserves special note.

Among the sixteen patients who had received iodine within the previous month, three with initial basal metabolic rates of +50, +85, +46 had a reduction to under +12 after, respectively, twenty-five, thirty-three, and thirty days of thio-uracil therapy. Two had slower responses, their initial basal metabolic rates of +55 requiring six weeks for reduction to +20. In six cases the results cannot with certainty be rated as better than fair because, although all improved and none exhibited toxic symptoms, thyroidectomy was undertaken before the full effect of thio-uracil could reasonably have been expected. In four cases, two of which have been included above, the benefits of preparation by bed rest, high feeding, and iodine administration had already been tried and found wanting. One of these four patients did not respond. One fifty-year-old female with preceding pulmonary tuberculosis treated by thoracoplasty and having critically reduced vital capacity, died during thio-uracil treatment; the post mortem diagnosis was cor pulmonale and bronchopneumonia. It was difficult to assess thio-uracil in this case. She had, however, no recognized thio-uracil toxicity and had gained seven pounds during forty-six days of its administration. Three patients exhibited toxic symptoms and the drug was discontinued, one of these having had a quite satisfactory response in the twenty-four days before toxicity was manifest. This well-assorted group of cases is not suitable for statistical analysis but does provide useful examples for consideration of this drug. Cases which illustrate special points are separately recounted.

Case 6.—Good response; previously on Lugol's solution.

This eighteen-year-old woman developed nervousness, muscular weakness, increased appetite, heat intolerance and palpitation four months prior to hospital admission. She had received Lugol's solution for three weeks before admission. There was a diffusely enlarged thyroid gland, tachycardia, high pulse pressure, prominent pulmonary conus, a systolic murmur at the cardiac apex, marked purposeless motion, smooth, moist skin, fine tremor of the hands and tongue, and exophthalmos. Certain details of the course of this patient are given in Figure 1. The basal metabolic rate fell in thirty-three days to +8 per cent with a weight gain of 20 pounds. No definite toxic manifestations occurred

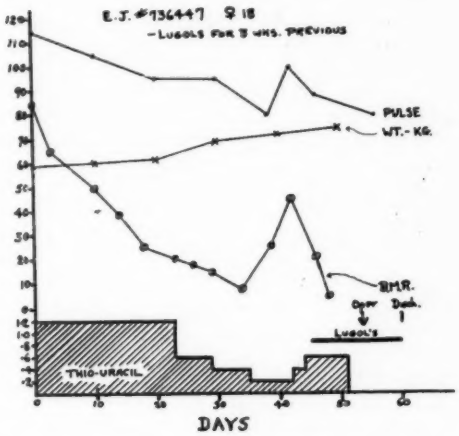

Fig. 1. Case 6. Good response in a previously Lugolized case. Note the escape with lowering of the dose. Thio-uracil charted as grams per day.

although the patient complained of tightness in the wrists and ankles. It will be noted that when thio-uracil was reduced to 0.2 gm. daily, there was a prompt elevation of pulse and metabolic rate. She tolerated a bilateral subtotal thyroidectomy well with no rise in pulse rate during a two-hour operation. Sixty grams of thyroid tissue were removed. The gland was friable and bled a great deal. Histologically there was marked hyperplasia such as is present in an untreated Graves' disease. Postoperatively her temperature rose to a high of 102.6° F. on the second, but was normal on the fourth day. Subsequent course has been very satisfactory.

The two following cases, illustrating special points for consideration, also showed a striking response.

Case 11.—Thio-uracil after failure of other therapy.

This sixty-eight-year-old woman had had a goiter all her adult life. During the five years prior to hospitalization, she had some heat intolerance, nervousness, sweating, dysphagia, dyspnea, hoarseness and a weight loss of 50 pounds. She had had recurrent attacks of right upper quadrant abdominal pain and fever associated with definite jaundice for two years. On examination she had a very large, stony-hard, irregular thyroid which extended substernally. There was stare and lid-lag. Her skin was warm, moist and moderately pigmented. The heart was normal in size; tachycardia and auricular fibrillation developed during her hospital stay. Preparation for thyroidectomy using iodine but no thio-uracil progressed well for several weeks but was interrupted by an attack of gall-stone

colic with fever, leukocytosis, severe anorexia and abdominal tenderness. She recovered incompletely from this and her hyperthyroidism was definitely aggravated in spite of continued use of Lugol's solution. Her basal metabolic rate which was + 38 per cent at time of admission, rose to + 46 per cent after the subsidence of fever. Physical exhaustion was marked and feeding was very difficult. Because of the progression of symptoms thio-uracil was started and she was given 1.0 gm. daily for thirty days after which time she was much improved clinically, and her basal metabolic rate was + 12 per cent. A left thyroid lobectomy was performed with removal of 270 gms. of adenomatous thyroid tissue. Her blood pressure rose to 220 systolic during the operation, but otherwise she tolerated the operation well. Her temperature rose to 102° F. postoperatively. but it was normal on the third day. She has not been back to clinic since discharge, but has written that she is feeling well and is able to do her own work. The histology of the thyroid tissue removed was that of an adenoma; there was considerable calcification.

This case is illustrative of four in our series in which thio-uracil has rescued an apparently hopeless situation. Its use in such cases is clearly indicated.

Case 2.—Long-maintained therapy.

This sixty-four-year-old woman noted dyspnea on exertion, nervousness, occasional palpitation, heat intolerance, profuse sweating and a ten-pound weight loss in spite of a good appetite for a year prior to hospitalization. She had definite symptoms of chronic sinusitis and had noted a flare-up of symptoms just prior to hospital admission. She had a tachycardia, increased pulse pressure, auricular fibrillation, left ventricular cardiac enlargement. Her eyes were prominent and lid-lag, stare and poor convergence were present. She had an assymetric nodular goiter. There was slight pitting edema of the ankles and legs, and the liver was enlarged. The mild evidence of heart failure responded to bed rest and digitalization. Having already been started on Lugol's solution she was given thio-uracil concurrently. She received 20 gms. of thio-uracil in twenty-five days in the hospital with very satisfactory response. Her basal metabolic rate decreased from + 50 per cent to + 12 per cent with corresponding clinical improvement. She refused operation and was discharged from the hospital with instructions to take 0.2 gm. of thio-uracil a day. On the first subsequent visit to clinic she exhibited definite evidence of recurrence of all her symptoms of hyperthyroidism so the dose of thio-uracil was increased to 0.4 gm. per day along with Lugol's solution. She improved very definitely again in two weeks and for eight months was then maintained on a dose of 0.2 gm. of thio-uracil without any Lugol's solution. Withdrawal of thio-uracil at that time resulted in a return of symptoms. The 0.2 gm. daily dose was again given and she has been maintained satisfactorily on it for a further two months. Auricular fibrillation disappeared spontaneously after two months of therapy. She complained of tightness and numbness of her feet on one visit but this complaint disappeared, and she has demonstrated no other toxic manifestations.

This is one of the two cases in which thio-uracil has been used successfully as maintenance therapy. The second case was in a twelve-year-old girl who had recurrent hyperthyroidism after thyroidectomy at the age of eight; the initial dose in this second case was 0.5 gm. with 0.1 gm. daily for maintenance. Williams and Clute have treated thirty-five patients with maintenance doses of thio-uracil for more than four months and sixteen patients for more than six months. Astwood[3] withdrawing the drug in eleven patients after six to nine months of treatment, found that continued remissions occurred, five of the patients being observed for longer than three months after the withdrawal. This suggests a new possibility for thio-uracil. However, our experience with withdrawal in this one case has not been successful and William and Clute had recurrences in all four cases where the drug was discontinued after "several months" of therapy. More evidence is obviously needed. As regards maintenance doses 0.1 gm. daily has sometimes[38] proved to be inadequate. On the other hand, with the 0.2 gm. dose[21,38], evidences of myxedema have developed.

Case 9.—Slow response; previously on Lugol's solution.

This fifty-one-year-old woman lost 20 pounds in five weeks following an attack of "flu." She had palpitation, heat intolerance, and muscular weakness for five years, but had been able to compensate apparently by an increased appetite. Before coming here she received Lugol's solution for one month irregularly because of nausea and vomiting induced by it. She had an assymetrically enlarged thyroid gland, marked brownish pigmentation of her skin, wavy and friable fingernails, and a tachycardia. The covers of her bed demonstrated the remarkable tremor of her hands and feet. Initial basal metabolic rate was + 57 per cent. She received thio-uracil for forty-two days with a fall of basal metabolic rate to + 17 per cent. A subtotal thyroidectomy was performed and the surgeon encountered considerable bleeding, which he thought was more than usual for thyroidectomy. Her postoperative course was uneventful. Sections of the thyroid revealed very small acini with many cellular areas without acini or colloid. It is possible that thio-uracil caused some nausea but no severe nausea or vomiting as was encountered with iodine.

This case represents about the average of successful responses in patients previously receiving Lugol's solution. Cases of this sort, still open to prolonged trial of bed rest, feeding, sedation, and iodine have not been classed with the four, of which Case 11 was an example, where thio-uracil may be fairly said to have come to the rescue. Nevertheless, it produced a satisfactory result and the advantage of a relatively normal metabolism at the time of thyroidectomy is not to be gainsaid. This advantage has been particularly welcome in other patients who had had cardiac decompensation during the course of their disease.

Case 3.—Failure to respond; previously on Lugol's solution.

This fifty-year-old woman had had pernicious anemia for four years. About nine months before hospital admission she had increasing nervousness, heat intolerance, tremor of hands, a good appetite, palpitation, dyspnea on exertion, and a weight loss of 30 pounds. Iodine was given for three months with initial improvement but with return to her former state prior to being seen here. She had a moderately enlarged firm diffuse goiter, a stare and lid-lag, tachycardia, a blood pressure of 158/98, a systolic murmur at base and apex of heart, muscle weakness, and warm moist skin. The initial basal metabolic rate was + 61 per cent. She received 1.0 gm. of thio-uracil for thirty-one days and 0.6 gm. for sixteen days, a total of seven weeks. There was a gradual weight gain from 85 pounds to 93 pounds but there was only moderate improvement in the basal metabolic rate to + 45 per cent. There was some clinical improvement. She tolerated a two-hour operation well and her postoperative course was uneventful. Thirty-eight gms. of thyroid tissue were removed and had the histologic appearance of regressing Graves' disease.

Because of concurrent bed rest and high caloric diet, it cannot be concluded that thio-uracil had any effect here. All of the cases recorded by Williams and Clute gave a satisfactory response in under seven weeks. Bartels[6], in treating severe hyperthyroidism preoperatively with thio-uracil, was satisfied to wait as long as six months and obtained satisfactory remissions in all cases. Paschkis, Canatrow et al.[21], finding 1.0 gm. as daily dose ineffective after several weeks, employed in three cases 2.0 gm. of the drug with subsequent full effect in a short period of time. The problem can be argued either way. It would seem that barring toxic reactions, enough drug for a sufficient period of time will eventually lower the basal metabolic rate. On the other hand, circumstances in the individual case may decide that the delay is inadvisable.

Toxic Reactions.—In our twenty-six cases, there were five toxic reactions for which it seemed necessary or wise to stop the drug.

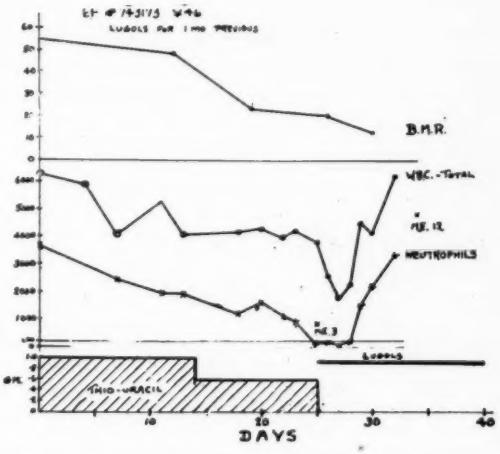

Fig. 2. Case 10. Leukopenic response to thio-uracil. ME indicates percentage of myelo-erythroid layer in sternal marrow.

Case 18.—Severe rash.

A seventy-two-year-old woman on the fourth day of 0.6 gm. daily dose of thio-uracil, developed a severe erythematous rash mostly on the face and upper trunk with edema around the eyes. The rash disappeared after stopping thio-uracil without discontinuing other therapy. She had previously manifested sensitivity to sulfonamide.

Case 10.—Leukopenia.

This forty-six-year-old woman developed symptoms of hyperthyroidism two years previously with progressive increase in symptoms during the six months prior to hospitalization. She had a diffusely enlarged thyroid gland, was very overactive, and had lid-lag, stare and poor power of convergence. She had received Lugol's solution for one month before coming here. She was given 1.0 gm. of thio-uracil daily for fourteen days and 0.6 gm. daily for ten days. Certain details are shown in Figure 2. She had a mild neutropenia during most of her treatment but severe neutropenia developed on the twenty-fourth day of treatment. Bone marrow biopsy at this time revealed arrest of the myeloid development at the myelocyte stage, with a myelo-erythroid layer of 3 per cent. Bone marrow biopsy performed ten days after the first one revealed a hyperplasia of all bone marrow elements with a rise of the myelo-erythroid layer to 12 per cent. Note the rise in neutrophils and total leukocytes after stopping thio-uracil. Her basal metabolic rate decreased from + 54 per cent to + 20 per cent with a correspond-

ing clinical improvement. Lugol's solution was administered for one more week and she had a subtotal thyroidectomy thirty-four days after starting therapy. She tolerated a two-and-one-half-hour operation well and her postoperative course was uneventful. Histologically the appearance of the thyroid was that of regressing Grave's disease with some areas of persistent marked hyperplasia.

She received undoubted benefit from the thio-uracil, but she also suffered a serious toxic manifestation which fortunately subsided promptly.

Case 13.—Purpura.

This twenty-one-year-old woman with moderately severe hyperthyroidism received 1.0 gm. of thio-uracil for fourteen days. It had to be discontinued because of the appearance of cutaneous purpura; thrombocytopenia (77,000 platelets), increased bleeding time, and positive cuff test were found. The purpura disappeared in a few days and the platelet count rose to normal. She had a follicular tonsilitis to complicate her course further, but now seems to be improving under more conservative therapy.

She received no benefit from thio-uracil and suffered a serious toxic manifestation which, however, cleared on removal of the drug. Purpura following thio-uracil has not previously been reported. Because of the possibility of thrombocytopenia, it certainly will be advisable to check for bleeding tendency before submitting any patient to operation.

Cases 14 and 25.—Increased bleeding tendency.

Both of these cases developed a markedly positive cuff test, one on the twenty-fourth and the other on the twenty-ninth day of thio-uracil therapy, 0.6 gm. being the daily dose. In view of the experience with Case 13, the drug was stopped in both.

In the first of these two cases, the white count at the time the drug was stopped was 4,500, with 41 per cent neutrophils and the platelet count was 350,000; after stopping the drug, the cuff test returned to normal. Iodine was started when the thio-uracil was stopped and a week later the basal metabolic rate was +12. No difficult bleeding was encountered at operation which was done sixteen days after discontinuing thio-uracil.

The second case had a negative cuff test before thio-uracil was started; it became progressively positive until the drug was discontinued; at this time the platelet count was 130,000 and the white cell count 3,000 with 52 per cent neutrophils.

It will be noted that two of these five reactions were in patients receiving the higher dose levels earlier employed; the remaining three toxic reactions received the lower dose now generally recommended. Other toxic reactions in our cases have been minor or questionable.

Williams and Clute[38] in their seventy-two cases, discontinued the drug in three cases and stopped it temporarily in others. Thirteen of their patients had some sort of untoward reaction ranging from mild to severe, the most important of which were, one agranulocytosis; three urticarias, one of these with painful swollen joints and one with fever; swelling of the legs associated with retention of sodium, chlorine, and water. Other reactions which disappeared despite continued therapy were, one leukopenia to 3,200 with 20 per cent granulocytes; four morbilliform rashes with itching; two nausea and vomiting; and one swollen, sore submaxillary gland. Bartels[6], in eleven patients with severe hyperthyroidism treated for from one to six months, encountered no toxicity. Paschkish, Cantarow, Rakoff, Walkling, and Tourish[21], observing twenty-one cases, noticed the appearance in three of rash, fever, arthralgia, leukopenia, jaundice. Soffer, Kert and Gabrilove[33], in twenty-five patients, encountered drug toxicity in five; two had mild leukopenia, one rash and fever, one edema, one conjunctivitis. Reveno[26], in recording his experience with nine cases, observed, in one instance, enlargement of the thyroid due to hemorrhage into its substance.

It is obvious that consideration of toxicity must be carefully weighed against certain undoubted advantages. Agranulocytosis and bleeding tendency would seem to be the most serious reactions so far encountered and it becomes an obvious requirement that patients be kept under close watch. A fatal case of agranulocytosis due to thio-uracil, has already been reported.[12]

Effect on Thyroid and on Eye Signs.—Since thio-uracil typically reduces colloid and results in cellular hyperplasia, increase or decrease in size of the gland might be expected, depending on the resultant of these opposing factors. In our cases no definite size changes have been noted in the gland. In two of them, however, there has been an increase in the bruit heard over the gland during the period when clinical improvement was manifest. Williams and Clute remark that changes in the gland are not easy to discern; they recorded enlargement in eleven of their seventy-two cases; the majority of the others, however, decreased in size. The possibility of en-

largement will, therefore, apparently have to be given practical consideration chiefly in cases where the gland has already encroached upon some surrounding structure. In our cases, eye signs have either improved or become no worse during treatment. Williams and Clute found that simple stare improved but that malignant exophthalmos which was originally present in five patients became worse. They used desiccated thyroid in the treatment of these. In other cases also thyroid medication has been used to induce a reduction of size in the thyroid gland. The rationale in both circumstances is the same, depending on the belief that circulating thyroid hormone keeps the pituitary in check. It is consistent with the observation[22] that administered thyroid does not produce eye signs whereas thyrotropic hormone does. The concept of using thyroid substance to control pituitary function has some reasonableness in the light of the studies by Means, Hertz and Williams[20] of dissociated oculopathy in Graves' disease. In this connection, too, it is interesting to note that Rienhoff[29,30], having observed the ability of administered thyroid to shrink colloid goiter, administered it to nine hyperthyroid patients; this treatment resulted in a reduction of the signs and symptoms of hyperthyroidism with shrinkage of the gland and an average fall in basal metabolic rate of 20 per cent. All patients did well postoperatively.

Thyroidectomy After Thio-uracil.—The use of thio-uracil in preparation for operation, judged by reports in the literature and in our own cases has, in general, given good results. The advantage of lowering the basal metabolic rate to normal or near normal has been reflected in smooth operative and postoperative courses. The main disadvantage so far encountered has been that in a few cases the gland has bled more easily than might otherwise have been expected; this difficulty has not been followed by any untoward postoperative results.

Histologic Changes.—In general[23,38], the gland, after thio-uracil therapy, shows hyperplasia with diminished colloid; but the picture varies considerably. In a few cases this appearance is quite striking. In others, particularly those previously treated with iodine and having a slow response to thio-uracil, the gland may present a picture of involution with minimal hypertrophy. Rawson, Evans, Means, et al.[23], did control studies in five cases, biopsies being taken before thio-uracil was started for comparison with the operative specimens. In three of these five cases there was no significant increase in the height of the cells as a result of the thio-uracil therapy; in the other two, there was a definite increase. All of these five patients responded well but the two which showed the increase in cell height had had the more prompt and complete clinical improvement.

Discussion

The foregoing presentation omits certain observations entirely, but does mention the chief points which are thought to bear significantly on the advisability or otherwise of thio-uracil therapy in hyperthyroidism.

Considering first those patients not previously treated with iodine, it would appear from the data of Rawson, Evans, Means et al.[23] on thio-uracil, compared to the iodine response curve of Means and Lerman[19], that for both agents approximately the same depression of basal metabolic rate is obtained in the first ten to twelve days. The difference would appear to be that by waiting longer, i.e., up to three to six weeks, thio-uracil, with great probability, will produce a more complete remission with presumably some lowering of subsequent operative risk. If the patient is ambulatory and can visit the doctor frequently, this waiting period may be worth while. Against this definitely must be put the possibility of toxic reactions. The incidence of toxic reactions necessitating withdrawal of the drug is apparently more than 10 per cent. For safety's sake, the visits to the physician should be at least weekly and should include a white and differential cell count and a cuff test. It will be noted from Figure 2, that even a weekly check might not have sufficed to catch the white cell depression in sufficient time. Although it is to be admitted that dependence on iodine has hazards of its own, the wisdom of using thio-uracil, instead of iodine in these cases, cannot be considered as established.

For cases previously treated with iodine there may, in many instances, be no choice and it is here that thio-uracil seems to have made the best contribution so far. It has been a welcome expedient in cases complicated with cardiac decompensation.

The advisability of continuous thio-uracil thera-

py to maintain a remission obviously requires further evidence. The hope of continued remission after eventual withdrawal of thio-uracil remains still a hope. The only reasonable attitude at the present time would seem to be one of caution. On the other hand, there is no call for pessimism because of the drawbacks encountered in this new line of therapy. The suggestion[10] that liver extract may cancel out the blood cell depression is a reasonable one and needs investigation. It is possible that an improved drug with lower toxicity may be found. The use of iodine therapy with or following thio-uracil therapy has not had, as yet, an adequate trial.

Summary

The literature on the experimental use of thio-uracil in the treatment of hyperthyroidism is briefly reviewed and illustrative cases from the experience at the University of Minnesota Hospitals are given. Although the ability of this drug to produce remission in hyperthyroidism is well established, particular attention is drawn to toxic reactions and to the necessity of keeping under close observation all patients who receive the drug. The advantages and disadvantages of its use are discussed.

The cases presented have been from the services of Dr. C. J. Watson, Dr. Irvine McQuarrie, and Dr. O. H. Wangensteen, whose co-operation, together with that of their staffs, is gratefully acknowledged.

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CLINICAL-PATHOLOGICAL CONFERENCE

MINNEAPOLIS GENERAL HOSPITAL

A. J. HERTZOG, M.D., Pathologist

MULTIPLE MYELOMA

Report of Three Cases

DR. HERTZOG: Today we are taking up three cases of multiple myeloma. I will briefly discuss some of the clinical and laboratory aspects and Dr. Schleicher will speak about the myeloma cells. Dr. Riley will give the history of the first case.

DR. RILEY: This is the case of an eighty-five-year-old white man who entered the Minneapolis General Hospital on September 27, 1943, with complaints of nosebleeds and weakness. He had had these symptoms for the past two years. The nosebleeds gradually increased in frequency. Physical examination revealed a poorly nourished white male whose pulse was 86, blood pressure 160/90 and temperature 96 degrees. Examination of the head and neck was essentially negative. The chest showed a flaring of the rib margins. The heart was slightly enlarged with a systolic murmur at the apex. The liver, spleen and lymph-nodes were not palpable. There was no edema of the extremities. Neurological examination was essentially normal. Laboratory examination on admission revealed a hemoglobin of 33 per cent, with 1,690,000 red blood cells, 7,900 white cells with 75 per cent neutrophiles, 22 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophiles. Bleeding time was more than ten minutes, clotting time two minutes, thirty seconds. The platelet count was 200,000 per cu. mm. Urinalysis on admission was negative except for one plus albumin. Serologic tests for syphilis were negative. Sedimentation rate was 167 mm. for sixty minutes (Westergren). Plasma proteins were 9.4 grams with 5.31 grams of globulin. The hemoglobin fluctuated between 33 and 40 per cent during his stay in the hospital. Blood morphology studies showed the red cell mean diameter to be 8 microns with marked anisocytosis present. Sternal biopsy was performed and the findings on this will be discussed by Dr. Schleicher. X-rays of the ribs, skull and long bones were taken. These will be shown by Dr. Stenstrom. The patient's course was frequently downhill, frequent nosebleeds occurred, he developed a septic temperature and expired on December 5, 1943. Permission for autopsy was refused.

DR. HERTZOG: Do you know what gave the lead to the diagnosis of multiple myeloma in this case?

DR. RILEY: All unexplained anemias that enter the hospital have sternal aspirations of the bone marrow. The sternal puncture made the diagnosis.

PHYSICIAN: I think you could consider multiple myeloma without the bone marrow findings in view of the high plasma proteins of 9.3 grams, particularly the elevated globulin fraction of 5.31 grams.

DR. STENSTROM: X-rays are a great deal of help in diagnosing multiple myeloma. Note the rounded areas of decreased density in the skull. I do not think from this film alone one can make a diagnosis, as the areas are not sharply demarcated. You must not confuse diploic markings. You also have to consider metastasis from a hypernephroma. The ribs show decalcification with a tendency towards punched-out areas. Occasionally all one gets in multiple myeloma is osteomalacia and osteoporosis. The areas have to be sharply reamed out to be diagnostic. Another favorite site for multiple myeloma is the lumbar spine. The dorsal spine in this case shows generalized osteoporosis with a tendency towards rounded areas, but not sufficient to be certain of the diagnosis. We do not have a picture of the lumbar spine. The femur is fairly normal. One area in the upper end of the radius is quite sharply demarcated. In conclusion, we have nothing except two punched-out areas in the skull and one area in the radius with generalized decalcification of the bones.

STUDENT: Would you make a definite diagnosis of multiple myeloma from the x-ray findings alone?

DR. STENSTROM: I would not. One must correlate the x-ray findings in this case with the laboratory work.

PHYSICIAN: I thought there was something in the long bone that was characteristic of multiple myeloma that distinguished it from hypernephroma metastasis?

DR. STENSTROM: Multiple myelomas have a tendency to expand the cortex at times without going through, while hypernephromas tend to follow the path of least resistance rather than expand the cortex of the bone. However, this distinction is not always too reliable.

DR. HERTZOG: We have two other cases. The first one is a fifty-eight-year-old woman who was admitted to St. Barnabas Hospital in 1942 for a cholecystectomy. The gall bladder was found to contain stones and old chronic inflammatory changes. She was readmitted for a perineorrhaphy in August of 1943. At this time she was found to be anemic with 59 per cent hemoglobin (Sahli). Following the last operation she

ran an unexplained fever. An x-ray of her chest was taken. This showed an area of rarefaction in the right clavicle that was considered to be a bone cyst at the time. The anemia persisted but no attempt was made to find the nature of the anemia. She was treated with liver and iron but failed to show any improvement. She was readmitted to the hospital in August, 1944, with a history of weight loss of 50 pounds, persistent anemia and pain in the arm. The technician had difficulty in making a blood smear on this patient because of the greasy nature of the blood. The red cell count was 2,780,000 and the hemoglobin was 50 per cent (Sahli). The white count was 6,900. The anemia was a normochromic type and the red cells showed marked rouleaux formation. This and the greasy smear were recognized as common in multiple myeloma. Hence the urine was examined for Bence-Jones protein. The Bence-Jones protein was absent and we forgot about multiple myeloma. The urine showed one to two plus albumin. Blood urea nitrogen was within the upper limits of normal. The patient was referred to physiotherapy. An x-ray of the shoulder showed findings compatible with multiple myeloma. Other x-rays showed widespread involvement of the skeleton. A bone marrow aspiration was then done. This was typical of multiple myeloma. The total plasma proteins were found to be 11 grams with 6.7 grams of globulin. Hence the diagnosis in this case was arrived at more or less in a roundabout manner. The earliest symptom was anemia and pain in her shoulder. The patient is still living.

The second case was that of a sixty-one-year-old man whose principal complaint was weakness and weight loss. He had a persistent albuminuria with casts, but the blood pressure was normal. An intravenous pyelogram was attempted but the kidneys did not visualize as no dye was excreted. However, Dr. Russel Morse picked up the findings of multiple myeloma in the bones of the lower trunk. We then began to investigate the case from the laboratory standpoint. Bence-Jones proteins were also absent, serum calcium was 17 mg., serum phosphorus and alkaline phosphatase were normal. Dr. Stenstrom called attention to the fact that in multiple myeloma the bones show marked decalcification. You usually find an elevated serum calcium associated with an excess amount of calcium excretion in the urine. The normal alkaline phosphatase points to an absence of osteoblastic activity. The blood urea nitrogen was 56 mg. per cent and creatinine was 2.2 mg. per cent. The plasma proteins were normal; globulin was only 2.5 grams. This shows all cases of multiple myeloma do not have an elevated plasma protein. A bone marrow aspiration was done and the typical myeloma cells were found in the sternal marrow. The patient expired at home and no autopsy was obtained. It would have been interesting to see what the kidneys would have shown as it would seem, in view of the normal plasma proteins and absence of Bence-Jones proteins, that something else besides simple blocking of the tubules of the kidneys by casts was present.

Microscopic Study

DR. HERTZOG: This is a photomicrograph of the blood smear in the fifty-eight-year-old-woman from St. Barnabas Hospital. This gave us the lead to the diagnosis of multiple myeloma. Note the marked rouleaux formation in the red blood cells. This is not pathognomonic. It simply means that you have an excess amount of serum protein. This rouleaux formation may be so pronounced that it is difficult to cross-match the patient for transfusions because of this auto-agglutination. It is always suggestive of multiple myeloma, as multiple myeloma is one of the commonest causes of elevated plasma proteins. At times this auto-agglutination may be noticed in the veins of the retina with an ophthalmoscope. The next photomicrograph is the bone marrow of the same case. It shows over 50 per cent of the cells to be myeloma cells with an eccentric nuclei and marked basophilic cytoplasm.

DR. SCHLEICHER: When Dr. Hertzog showed me this slide, I ventured the opinion that the patient probably did not have Bence-Jones protein in the urine. This statement was made on the basis of the uniformity in size of the so-called plasma cells and deep blue stained cytoplasm. For some reason, the globulin in the myeloma cells during this particular phase of the growth of the tumor is not of the proper chemical composition to be secreted by the cell. When the cells secrete globulin, they become larger and vary in size. The cytoplasm appears to be vacuolated and stains irregularly. In my series, the type of tumor shown on the screen failed to show Bence-Jones protein in the urine. It appears to be a slow-growing type of tumor. Solitary types of myeloma produce much rarefaction of the bone and are easily picked up by the roentgenologists. The solitary types are of a high degree of malignancy. The myeloma cells arise from the reticulum of the bone marrow and have no connection with the ordinary plasma cell. This excellent colored photomicrograph made by Dr. Hertzog shows the development of the myeloma cells from a small lymphoid reticulum cell. It should be kept in mind that the activity of the tumor varies, and, therefore, one examination may fail to show Bence-Jones protein in the urine; a series of examinations may yield a positive specimen.

DR. HERTZOG: The history of multiple myeloma goes back many years. Bence-Jones in 1845 described the peculiar protein in the urine in cases of so-called mollities ossium. This peculiar Bence-Jones protein is found on heating the urine to 50 or 60 degrees. When the urine is brought to a boil, the precipitate disappears and only reappears on cooling. When albumin is present in addition to Bence-Jones protein, the two must be separated. Von Rustizky in 1873, gave the disease the name multiple myeloma. Kahler, in 1889, deserves the credit for connecting Bence-Jones protein with the disease and describing many of its clinical aspects. It is sometimes called Kahler's disease. Wright, in this country in 1900, showed the morphological similarity of the myeloma cells to plasma cells. The clinical aspects of the disease are quite varied. A frequent symp-

tom is painful back or bones in a middle-aged or older person. This is commonly called neuritis. Paraplegia occurs at times due to a lesion of the vertebral body pressing on the spinal cord. A pathologic fracture of a rib is always suggestive. At times the patient himself may notice multiple small tumors along various bones. An albuminuria with a normal blood pressure and especially with a hyperproteinemia is suggestive. The widespread use of x-ray picks up many of these cases. Unfortunately, Bence-Jones protein is only found in around 50 per cent of the cases. It may be higher if repeated attempts to demonstrate this protein in the urine is done.

PHYSICIAN: I would say well under 50 per cent of cases fail to show Bence-Jones protein.

DR. HERTZOG: I would like to ask Dr. Schleicher whether the few plasma cells found frequently in the blood smear in these cases of multiple myeloma have any diagnostic significance?

DR. SCHLEICHER: I do not think so. Plasma cells originate from many sources. If you mean myeloma cells, that is different.

STUDENT: What percentage of cases of multiple myeloma do you think can be picked up by a single aspiration of the sternal marrow?

DR. SCHLEICHER: With the exception of the rare solitary myeloma, I think you will pick them all up. I will show a photomicrograph of the bone marrow of another case. This color slide shows several myeloma cells with the characteristic globulin crystals of Bence-Jones protein within the cytoplasm of the cell. The crystals are either needle-form or rhomboid. This was a highly malignant tumor. Bence-Jones protein was found in the urine daily. Wintrobe and von Bensdorff et al. observed globulin crystals in the plasma and serum in their cases. One can estimate to some extent the clinical degree of malignancy by the amount of secretory activity of these cells. I have already stated that the myeloma cells arise from the reticulum. This slide shows myeloma cells arising from vascular adventitial cells considered undifferentiated reticulum cells. The scattered small groups of myeloma cells show the disseminated character of the growth. This is why a single aspiration of the marrow will yield diagnostic cells. Of course, in the rarer solitary forms, one must aspirate at the site of the tumor. Multiple myeloma is a distinct clinical entity and a neoplasm.

DR. HERTZOG: Is there a close connection between multiple myeloma and leukemia?

DR. SCHLEICHER: Yes, there is. Sometimes when the myeloma cells enter the circulation due to a rupture of the sinuses of the marrow from the pressure of the growing tumor, the disease resembles leukemia.

DR. HERTZOG: All of the elevated serum globulin in these cases is not entirely of the Bence-Jones type, is it?

DR. SCHLEICHER: That is not known. Investigators differ on this question. Many believe that globulin is formed in the bone marrow as well as in the liver. This slide shows an intermediate form of plasma cell observed in the bone marrow of a case of myeloid leukemia. This type of cell is believed by some investigators to produce globulin under physiologic conditions. In myelogenous leukemia there is occasionally a high serum globulin and a trace of Bence-Jones protein in the urine. Whether this intermediate plasma cell secretes the globulin is a question still to be answered. I have observed no crystals in this type of cell.

DR. RILEY: Have you attempted to find these globbulin-producing cells in the liver and spleen?

DR. SCHLEICHER: Up to date I have not been successful.

DR. HERTZOG: Dr. Schaaf, would you like to make any comment?

DR. SCHAAF: We see only about one case of multiple myeloma in three years, and I do not have anything to add to this discussion. How many cases of multiple myeloma do you see in this hospital?

DR. SCHLEICHER: We saw three cases in one and one-half years.

PLASMA AND TISSUE PROTEINS APPEAR INTERCHANGEABLE

Plasma and tissue proteins should no longer be considered as distinct entities. Evidence cited editorially in the Winter, 1945, issue of *The Journal of Parenteral Therapy* strongly suggests that there is a continuous and rapid interchange—or traffic—between them. Under conditions of inadequate or restricted protein intake, 1 Gm. of plasma protein (albumin) is lost for every 25 to 30 Gm. of tissue protein. The same ratio holds true when the attempt is made to replace plasma protein and tissue protein by restoring an adequate protein intake. In patients with serious protein depletion owing primarily to malnutrition it is highly impractical to make use of human plasma or serum transfusion.

CLINICAL-PATHOLOGICAL CONFERENCE

ST. LUKE'S HOSPITAL—DULUTH
ARTHUR H. WELLS, M.D., Pathologist

Report of Case

DR. T. O. YOUNG: A thirty-four-year-old white male mechanic was found to have an intrathoracic shadow suggestive of a tumor during a routine x-ray examination by the St. Louis County Mobile X-ray Unit five months before his death. It was then learned that for the past two or three years he had had a hacking cough occasionally productive of clear, serous sputum. He smoked from one to two packages of cigarettes a day. There had been mild aches during the past few months with twisting and prying sensations over the right scapular area. There was no loss of weight. The physical examination was entirely normal excepting for bronchial breathing in a small area posteriorly over the right lung. There were also a few crepitant râles in the bases of both lungs. His weight was 230 pounds. Blood pressure was 130/84 and routine laboratory studies were essentially normal. On the eleventh day before his death a tumor mass about the size of a goose egg was removed by a transthoracic posterior route by Dr. T. J. Kinsella. The mass was attached to the parietal pleura at the level of the third rib posteriorly on the right side. It protruded almost entirely into the pleural cavity. The patient appeared to be doing well excepting for a low-grade fever between 100° and 101° F., and a pulse rate between 110 and 120 per minute. Respirations were between 30 and 40 per minute during this period. There was a leukocytosis reaching a height of 24,000 and then subsiding to 16,000 on the day of his death. A low-grade anemia was also noted following the operation in spite of three blood transfusions of 500 c.c. each. There was frequent coughing sometimes productive of a small amount of mucoid sputum. On the third postoperative day aspiration of much mucus from his bronchi gave him immediate relief from a brief period of cyanosis and dyspnea. Restlessness and profuse perspiration were noted. Sulfathiazole grams 5 were used in the pleural cavity at the time of the operation and later 7 grams of sulfadiazine were given by mouth. Blood levels of the sulfonamides were not determined.

The patient's general condition was considered satisfactory until two hours before his death when he suffered from an attack of cyanosis, rapid, weak pulse and severe dyspnea. Respirations at this time reached 40 and pulse 120 per minute. After about fifteen minutes the attack subsided and he joked with the intern. However, shortly before his death he again developed severe cyanosis, rapid, weak pulse and dyspnea. He was rushed to the operating room for bronchoscopic aspiration only to die before the procedure could be accomplished.

Surgical Specimen

DR. A. H. WELLS: The resected mass was irregularly oval in shape, had a thin, distinct capsule and measured 4.5 by 6.5 by 7 cm. The site of attachment measured 4.5 cm. in diameter. The cut surface was gray, fibrous, glistening and almost homogeneous. Briefly, the microscopic picture (Fig. 1) was that of a lymph-node with quiescent lymph follicles and no sinusoids. Rare nerves, made up from 75 to 150 myelinated fibers, coursed through the mass. Dr. Paul Klemperer felt that it was a nonspecific granuloma. Dr. M. B. Dockerty favored an inflammatory lesion. Dr. A. C. Broders' diagnosis was chronic adenitis. Dr. J. S. McCartney and Dr. George Berdez thought it best to fit the diagnosis of Hodgkin's disease while Dr. E. T. Bell favored leukemic infiltration. My diagnosis was a simple benign lymphoma on the basis of a congenital defect or hamartoma.

The case is now open for diagnoses from the audience.

PHYSICIANS: "Death by pulmonary embolus." "Coronary thrombosis." "Spontaneous pulmonary atelectasis."

Autopsy

DR. A. H. WELLS: The essential gross findings were those of changes in the heart, an infected operative wound, and moderate evidence of toxic changes in the various organs. The heart weighed 390 grams. All four cavities were mildly dilated. The musculature of both ventricles was flabby, distinctly pale and slightly mottled. There was no coronary sclerosis. Pericardial and endocardial surfaces were transparent. The four valves were free from fibrosis and vegetations and were apparently competent. There was a grade II diffuse congestion of the lungs throughout all lobes, somewhat more severe in the dependent portions. A mild patchy injection in the large air passages was noted but practically no mucus or pus was found in them. There was no pulmonary emboli and no areas of atelectasis. The liver, spleen and kidneys were all distinctly swollen, flabby, friable and revealed other evidences of moderate toxic changes. There was a suppurative process on the pleural surface of the operative wound extending its entire length and involving adjacent tissues for a distance of about 1.5 cm. on either side of the wound margins. In this area there were a few small pockets of thick, grayish, purulent matter and some induration and injection of surrounding tissue. Cultures revealed staphylococcus aureus and nonhemolytic streptococci. Postmortem blood cultures tak-

Fig. 1. Atypical lymph node structure.

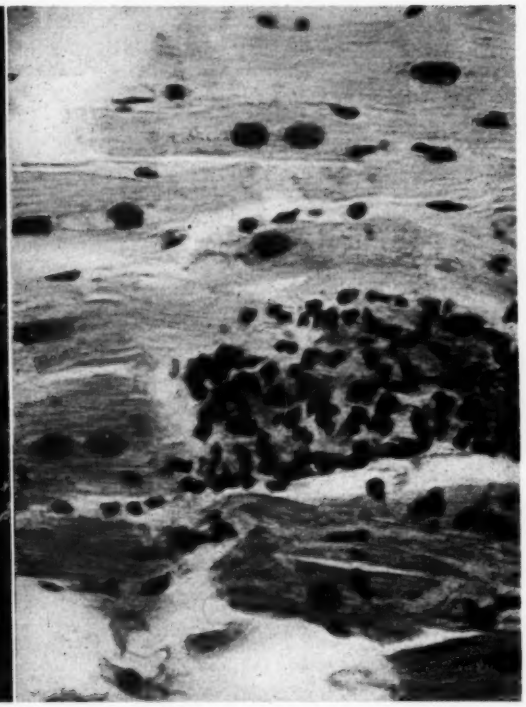

Fig. 2. Granular necrosis of muscle fiber with neutrophilic infiltration.

en twelve hours after death contained contaminating organisms.

The microscopic study confirmed the evidence of toxic changes in the liver, spleen, kidneys and heart. The bone marrow and lymphnodes were normal. Sections from various parts of the myocardium revealed scattered occasional small segments of muscle fibers (Fig. 2) undergoing a granular degenerative change similar to that of Zenker's hyaline necrosis associated with local moderate neutrophilic infiltration. There was a mild diffuse interstitial inflammatory reaction with occasional neutrophiles, monocytic cells and eosinophiles.

Discussion

DR. R. J. DAVIES: This case has two unusually interesting features, that of the immediate cause of death and that concerned with the histologic nature of the intrathoracic tumor. I am satisfied that the patient died as a result of the acute diffuse myocarditis which was very likely caused by the sulfonamide therapy. It may be argued that a septicemia or toxins from the infected operative wound were the cause of this cardiac ailment; a theory which cannot be disproved. This is the third patient I have seen die of isolated myocarditis resulting from sulfonamide therapy.

DR. A. H. WELLS: The various sulfonamide drugs used in therapeutic dosage have been indicated as the cause of death through inflammatory, degenerative and necrotic changes in the kidneys, bone marrow, blood, skin, liver, blood vessels, lungs, brain and myocardium.[13,23] In the kidneys[17] the mechanical obstruction by crystals of the drugs in the tubules, pelvi and ureters as well as the degenerative and necrotic changes in the tubules leading to anuria and subsequent uremia are relatively frequent and generally appreciated as are the widely used prophylactic measures of adequate fluid intake and output, alkalinization of the urine, routine microscopic study of the urine for red blood cells, routine blood level studies and avoidance of the use of the sulfonamides in patients with renal disease.

Fitz-Hugh[7] ascribes aplastic anemia, hemolytic anemia, thrombocytopenic purpura, agranulocytic angina and leukemoid reactions to sulfanilamide. He feels that they are sensitivity reactions similar to those due to aminopyrine and other drugs. Agranulocytosis[2,9,12,21] resulting from sulfonamides and the approximately 70 per cent fatal outcome are well known and guarded against by running routine daily white blood cell counts. Death in these cases appears to be due to loss of resistance to infections and according to Nixon, Eckert and Holmes[18] may be avoided by reinstituting the sulfonamide therapy in cases where a serious infection establishes itself. Penicillin might also be used to protect these patients until the infection subsides. In several reported cases of agranulocytosis autopsies revealed

a complete absence of granulocytes in the bone marrow with an arrest of maturation of the precursors of the granular series. In the rare cases of death resulting from acute hemolytic anemia[14,19] there has been found an erythropoietic hyperplasia of the bone marrow. Milder forms of hemolytic anemia are quite common. Fortunately anemias due to sulfonamides improve rapidly after discontinuance of the drug. Daily red blood cell counts are essential to avoid this complication. Skin reactions are indeed common while deaths as the result of severe exfoliative dermatitis[11] must be extremely rare.

Among the rare and probably less widely known complications of sulfonamide therapy, leading to death, are those lesions involving the liver, blood vessels, lungs, brain and myocardium. There have been described lesions from the liver varying from mild acute hepatitis with varying degrees of degenerative change of liver cells to acute yellow atrophy with extensive necrosis of parenchymal tissue.[1,6,10] Hyperbilirubenemia and the resultant jaundice are expected laboratory and clinical manifestations. A punch biopsy in a recent case proved the diagnosis of diffuse toxic hepatitis in one of our patients and saved the woman a surgical exploration. Periarteritis nodosa type of reaction involving the lungs, liver, spleen and kidneys has been described by Rich[20] and Duff[4] as resulting from sulfo therapy in a previously healthy man with a fractured tibia and fibula. Merkel and Crawford[16], also Lederer and Rosenblatt[15] described four deaths each occurring after sulfathiazole therapy in which there were focal areas of necrosis scattered through the lungs. No bacteria were found. The clinical manifestations of cerebral injury as the result of sulfonamides have included dysmorphopsia, aphasia, agraphia, stammering, toxic psychosis, peripheral neuritis, encephalomyelitis, myelitis, optic neuritis, transitory myopia, meningeal signs, blindness and convulsions. These symptoms and signs generally subside with discontinuance of the drug and death is rare,[5,22] There have been found areas of softening with ballooning of the myelin sheaths, proliferation of microglial cells, focal areas of necrosis and perivascular hemorrhages. Hyperplastic or necrotic changes in the endothelium of blood vessels of the brain may be the precipitating factor of many cases showing cerebral manifestations as the result of interference of blood flow.

Although there had been demonstrations of myocardial changes as a result of sulfonamide therapy in experimental animals, it remained for French and Weller[8] to discover the frequent (approximately 50 per cent) occurrence of a diffuse myocarditis in patients receiving any of the commonly used sulfonamides. Age and sex were not important factors. The dosage varied from 5 to greater than 200 grams over a period of from a few hours to several months. They found 126 cases of diffuse myocarditis in a properly selected group of postmortem examinations. Sulfonamide therapy was the only common factor in the group. The lesion was a perivascular infiltration by mononuclear phagocytes and eosinophiles. In more severe cases the infiltration became diffuse. Segments of cardiac muscle fibers underwent Zenker's hyaline degeneration. Animal experiments verified their conclusions as to the relationship between the sulfo drugs and myocarditis. Dozzi[3] described alterations in electrocardiograms of patients receiving sulfonamides.

Summary

An acute isolated myocarditis followed the use of sulfathiazole and sulfadiazine in the care of a patient with an intrathoracic lymphoma. Besides the comparatively frequent deaths from kidney complications and agranulocytosis resulting from sulfonamides there are rare fatalities because of lesions in the skin, brain, red blood cells, lungs, liver and blood vessels. The relative importance of acute myocarditis caused by sulfonamides needs further appraisal.

Diagnoses: (1) Intrathoracic lymphoma; (2) Acute sulfonamide myocarditis; (3) Infected operative wound of thorax; (4) Toxic changes in liver, spleen and kidneys.

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HISTORY OF MEDICINE IN WABASHA COUNTY

(Continued from November issue)

Biographical Dictionary

Francis Henry Milligan was one of the first and one of the most honored physicians in the state. He was born in Philadelphia in 1829, graduated from Jefferson Medical College in 1851, practiced for two years in Saint Louis and then located in Wabasha where, with the exception of one year spent in Hastings (1857), he remained until his death in December, 1888. He was the first physician in Wabasha, and his practice covered a very wide extent of territory. In addition to his professional duties, he served the county in the early days of its organization as treasurer (1853-60), in place of C. Shiveley, who had been elected, but who had never qualified; as sheriff (1854), in place of Levi Murphy, who was not a resident of the county; and as register of deeds (1855), when he finished a term for which Alexis P. Baily had been elected. During the Civil War, he served as assistant surgeon of the Third Volunteer Regiment of Minnesota Infantry and later as assistant surgeon in the Tenth Regiment. For many years he served as Wabasha city physician and as a county physician. He was active in local Democratic politics. He was appointed a United States pension agent, was president of the Mississippi Road, Bridge and Ferry Company, incorporated in 1877, and a member of the military Order of the Loyal Legion. He was elected mayor of Wabasha (1879) and was also a representative of the state legislature (1887).

In 1860, Doctor Milligan tried to interest practitioners in Wabasha County and vicinity in organizing a medical society. A fee table was adopted but no real organization was formed at that time. He was a charter member, later, of the Wabasha County Medical Society and a member of the Minnesota State Medical Association. He was president of the county organization in 1869-70 and president of the state organization in 1876-77.

Among articles, of which he was the author, were "Fracture of the Skull and Loss of Brain," published in the *Cincinnati Lancet and Observer* (May, 1867), and, in the same journal, the article entitled, "Will Uterine Leucorrhoea or Purulent Discharge from the Womb or Vagina, Produce Gonorrhoea?" (Oct., 1866).

W. F. Milligan, son of F. H. Milligan, was born in the town of Wabasha in 1870. He located in Millville to practice medicine following his graduation from the Ohio Medical College, Cincinnati, in 1892. In 1895 he moved to Wabasha where he soon became recognized as one of the leading physicians. He served on the pension board, and was a member of the Wabasha County Medical Society, and the state medical association. In 1896 he was elected a representative to the state legislature. In 1898, when the St. Elizabeth Hospital was opened in Wabasha, Dr. Milligan was put in charge.

In 1900, Governor Lind appointed him a member of the commission to investigate and direct the management of the state insane asylums. He died in 1905.

Benjamin F. Mott came to Lake City in 1887 from Fergus Falls. He was a member of the pension board in both towns. He received his medical training from the Eclectic Medical Institute in Cincinnati, from which he was graduated in 1874. He left the county about 1894.

E. S. Muir practiced in Plainview from 1894 until 1898 when he moved to Winona. He was a member of the Wabasha County Medical Society.

R. N. Murray, Lake City, began to practice about 1868; but for a number of years, he devoted much of his time to the milling business. He was a charter member of the Wabasha County Medical Society, serving as president in 1871, and became affiliated with the state association in 1872. He left Minnesota in 1875.

G. Nicolai practiced in Lake City in 1878.

Edward A. Patton, son of George R. Patton, graduated from the Miami Medical College in 1880 and practiced for two years in Lake City with his father before moving to Minneapolis.

George R. Patton was born in Allenville, Pennsylvania, in 1834. He received degrees from Miami Medical College (1855) and the Medical College of Ohio (1858). He was connected with Miami Medical College, was the author of a number of medical brochures, invented some instruments, and became well known as a physician and surgeon. His career in Lake City, from 1871 until his death in 1909, was largely that of a retired practitioner, doing skillfully the work which came his way but not reaching out for more worlds to conquer. He was elected to the county medical society in 1871 and the state association in 1872. The *Cincinnati Lancet and Observer* (April, 1876) contains an address by Doctor Patton before the Miami Medical College, Cincinnati, at its annual meeting.

J. F. Percy came to Mazeppa from Oronoco, Minnesota, about 1885 and moved to Los Angeles about 1890.

L. C. Perrine, an eclectic physician according to his card, located in Lake City in 1861. He ran a drug and variety store for a number of years.

M. T. Perrine was associated in business with the above. It is doubtful if he practiced medicine.

D. T. Phillips practiced in Lake City in 1876. He was a homeopath.

P. C. Remondino, a graduate of Jefferson Medical College, began to practice medicine in Wabasha in 1865. He had formerly been a surgeon in the army during the Civil War. For two years he was a partner of F. H. Milligan, with whom he had previously studied. He served as coroner, city physician, and chief of police. In 1867 he started a drug store in the city to which he devoted a share of his time. The following year he announced that he would give his attention to the homeopathic treatment of diseases. This was prob-

ably in answer to local demand for a practitioner of that school. He was a charter member of the Wabasha County Medical Society and became affiliated with the state society in 1871. He left Wabasha in 1874 and later settled in California.

It is interesting to note that he served as a surgeon for about six months in the French army during the Franco-Prussian war.

W. H. Rice was a homeopathic and hydropathic physician who practiced in Lake City in 1861.

F. L. Richter graduated from a German university and opened an office in Wabasha in 1886 where he remained for several years.

D. H. Roberts practiced in Plainview from 1870 until 1872, when he went to Owatonna.

H. N. Rogers began to practice in Zumbro Falls about 1878. In 1800 he was elected to the county medical society. About 1886 he left Wabasha County, and later practiced in Farmington, Dakota County.

O. Schmidt was a German physician and oculist who settled in Wabasha in 1874.

J. E. Schneider practiced in Lake City for a short time during the nineties. He was a member of the county medical society.

C. Q. Scoboria practiced in Mazeppa from 1892 until about 1896. He was a member of the county medical society.

J. A. Slocumb came to Minneiska in 1895, and after a few months moved to Plainview where he practiced in partnership with Dr. Tefft, and later with Dr. Muir. He was a member of the Wabasha County Medical Society, and was elected president of the organization in 1900 and twice thereafter. He remained in Plainview, where he became prominent as a physician and citizen. He died July 3, 1941.

Charles Snyder practiced in Wabasha in 1865.

H. W. Spafford began to practice in Lake City in 1865. He was a charter member of the Wabasha County Medical Society and its president in 1872. In 1874 he moved to Alma, Wisconsin. He received his training from Queens College, Canada, and the Ophthalmic Infirmary of New York. He was born in Ontario, Canada, April 27, 1828. He died November 24, 1877, and is buried in Lake City.

E. C. Spaulding, a graduate of the University of Vermont, formed a partnership in 1868 with G. W. Green, an eclectic, in Lake City. The next year he became the editor of the *Lake City Leader* and devoted most of his time to newspaper work until the fall of 1874. Apparently he left Lake City soon afterwards. In 1878 he was in the drug business at Northwood, Iowa.

C. C. Stauff and **F. H. Stauff** ran a drug business in Wabasha, in 1879, which they moved after a year or so to Lake City. Apparently neither was actively engaged in the practice of medicine.

J. Jerome Stone of Wabasha served as an assistant surgeon during the Civil War, studied with P. C. Remondino, and graduated from Rush Medical College in 1873. He did not immediately begin to practice in Wabasha and several times he left for short periods, intending to locate elsewhere. In 1874 he was elected to membership in the county society, and the following year to the state medical association. He practiced with his brother-in-law, F. H. Milligan, from 1880 until the spring of 1882. He served as president of the school board and was the proprietor of a drug store in Wabasha.

Nathaniel S. Tefft came to Minneiska in 1855 and moved to Plainview in 1860. He was one of the first physicians in the county and he remained there, a well-known figure, until his death half a century later. He graduated from the Eclectic Medical Institute of Ohio in 1852.

Doctor Tefft took an active part in the life of his community. In the early days, he was an officer in the local agricultural society, lectured before the Wabasha Literary Society and belonged to the Old Settlers Society. He held many offices in the Plainview I.O.O.F., serving as Grand Master of the Grand Lodge of Minnesota I.O.O.F. from 1884 to 1888. Throughout his career, he was very active also in local Republican politics, attending county and state conventions. He was very much interested in the labor unions. He was a member of the House of Representatives in the first state legislature, and was elected again in 1861. In 1871 he was a member of the Senate.

He was one of the first members of the Wabasha County Medical Society and served as president in 1871, 1888 and 1895. He was also a member of the state association (1871). He served many times as county physician, and in 1884 he was appointed a trustee of the Minnesota Hospital for the Insane. He died January 20, 1905.

John Tenny received his degree from Rush Medical College in 1899, and began to practice in Kellogg the following year.

Edgar Thorn, a homeopathic physician, practiced in Wabasha from September, 1878, until the following May, when he moved to New York.

Mrs. M. S. Tilson, a homeopathic physician, practiced in Lake City. She came to Lake City in 1862.

F. C. Titzell came to Lake City in 1891 from Ottawa, Illinois. He belonged to the homeopathic school. In 1894, and again in 1895, he was elected mayor of the city. He left in 1896, to accept a teaching position in surgery at a homeopathic medical school in Chicago.

Charles W. Tinker practiced in Wabasha for a short time before moving to Stewart, Minnesota, in 1879. He was a graduate of Jefferson Medical College and was elected to the Wabasha County Medical Society and the Minnesota State Medical Association in 1878.

E. A. Tupper practiced with Doctor Milligan in Wabasha from 1875 until 1878, when he moved to Zumbrota, Goodhue County. In 1875, he was elected to the Wabasha County Medical Society and to the state association.

Frederick W. Van Dyke, Wabasha, graduated from Bellevue Medical College in 1875. He was for seven years a partner of W. L. Lincoln, and the

professional card which they published at that time read, "consultation in German or English." In 1879, he assisted Doctor Lincoln in the first laparotomy performed in the county. He was a member of the county medical society (1874) and the state association (1875).

C. D. Vilas graduated from the University of Vermont in 1846 and came to Lake City in September, 1856. He moved to Michigan for a short while but returned to Lake City. He served as city health officer and as a county physician for several years. He was a member of the Wabasha County Medical Society. He died at about eighty-five years of age in 1907.

John P. Waste came to Plainview about 1866. He had formerly been a surgeon in an Ohio regiment during the war. He was elected to the Wabasha County Medical Society at its first regular meeting, and was elected to the state association in 1871. He was active in Republican politics, a member of the school board, a member of the Plainview city council, and a member of the state Senate (elected in 1873). In the last named capacity, he introduced bills for the publication of mortgages and registration of births and deaths. He continued to practice in Plainview for many years. He was elected president of the county medical society in 1898. He died in 1906.

— **Ware** practiced with Dr. E. O. Baker in Lake City in 1876.

T. R. Watson began practice in Zumbro Falls about 1897. He was a member of the county medical society.

G. C. Wellner practiced in Wabasha in 1889, and moved to Red Wing. (See Goodhue County)

Isaac J. Wells was a charter member of the Wabasha County Medical Society. He practiced in the city of Wabasha for several years.

— **Westfall** was a homeopath who practiced in Plainview in 1865 and moved to Rochester the next year.

J. L. Whitmore lived in Wabasha but apparently did not practice medicine. He ran a drug store during the first few years of the sixties and later started a tin shop.

Mrs. Mary Whitney, known as a specialist in the diseases of women and children, practiced in Lake City in the seventies.

Wm. F. Wilson was born in 1864. He graduated from the Chicago Medical College in 1891. He spent two and a half years as resident physician at the state school for the feeble-minded at Faribault, and then located in Lake City in April, 1894. In 1896 he was elected secretary of the Wabasha County Medical Society, a position which he has held for nearly fifty years. He is also a member of the Minnesota State and the American Medical Associations. He was appointed on the board of pension examiners for Wabasha County in 1897 and again in 1914. He has been president of the Lake City Public Library Board since 1906. Some of his published papers and articles are as follows: "Causation of Idiocy and Feeble-mindedness" in the *Proceedings of the Second Conference of Corrections and Charities,* 1894; "Notes on Epilepsy," *Northwestern Lancet,* 1895, "Differential Diagnosis between Variola

and Varicella," *Northwestern Lancet,* 1900; "Report of a Case of Eclampsia," *Northwestern Lancet,* 1903; "Treatment of Diabetes Mellitus," *Journal-Lancet,* 1915; "Yeast Infection of the Throat," *Journal-Lancet,* 1916.

I. C. Woodford was a homeopathic physician and surgeon who moved to Lake City in 1877 and remained about a year.

J. W. Woodworth was a botanic physician in Lake City in 1861.

Of all the physicians mentioned in this historical sketch only three, so far as is known, survive. They are Drs. W. J. Cochrane and Wm. F. Wilson of Lake City and Dr. Leonard E. Claydon of Red Wing.

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*The article on the medical profession in this history was formally repudiated by the Wabasha County Medical Society at a meeting held in June, 1884.

President's Letter

APPRECIATION

I wish to take this opportunity to express to the membership of the Minnesota State Medical Association my great appreciation for extending me the honor of being made president of the Association during the past year.

The performance of the duties of this office has been made very pleasant because of the wholehearted co-operation of the membership as a whole.

I have attended as many of the county and district meetings as possible, but the difficulty of transportation during this wartime period has limited to some extent the carrying out of this part of my program.

It has been a matter of great satisfaction to see the widespread interest the medical men of the state have shown in the various meetings, in spite of their being busier and of having to travel many miles often, to these meetings. This is one of the duties that has been assumed by the older men in place of the younger colleagues who are serving with the armed forces. Their ranks are terribly thinned. Their hours and responsibilities are multiplied, but they are carrying on uncomplainingly. For the most part, Minnesota people have not suffered for lack of medical care when they needed it.

Many men who had retired or nearly retired from practice are back in full harness now —taking the night calls and the long trips they had relinquished to the younger men. To these men I offer a HEARTY SALUTE!

I wish to thank the chairmen and members of all the committees for the efficient manner in which they carried out their duties. We are also very proud of the extensive activities of the Woman's Auxiliary during this wartime period. I am sure the organization will continue this activity after the war emergency has passed.

Unless one has had some contact with the central office of this Association, one has no idea of the amount of work that is carried out by this agency. The staff, headed by our efficient Executive Secretary, Mr. Rosell, is one of the more efficient organizations of its kind. Without the help and experience of its members it would have been much more difficult to satisfactorily carry out the duties that fall to the President of the Association.

Before turning this page over to my successor, Dr. E. L. Tuohy, I wish again to thank all members for their hearty co-operation during the past year.

E. Bruce Jones

President, Minnesota State Medical Association

Editorial

CARL B. DRAKE, M.D., *Editor;* GEORGE EARL, M.D., HENRY L. ULRICH, M.D., *Associate Editors*

THE PHYSICAL FITNESS PROGRAM

THE rejection of roughly a third of the draftees for military service has attracted public attention. In an effort to correct the situation, the President, in April, 1943, appointed a Committee on Physical Fitness in the administrative office of the Federal Security Agency. This Committee and its National Council on Physical Fitness presented a proposal to the American Medical Association to join in a program specially emphasizing the importance of physical fitness. This was accepted in June, 1944, and resulted in a Joint Committee on Special Emphasis for Physical Fitness.

Physical fitness has two rather distinct phases. One depends on physical education and the other on health. The medical profession is devoted to the subject of health and should wholeheartedly join in the Physical Fitness Program.

It was found that a large percentage of those who met the requirements for military service were not physically fit to make good soldiers. They were lacking in muscular strength, agility, and endurance, and required several months of training before they were in condition. There was evidence of need for improvement in the physical education even of recent high school graduates, 50 per cent of whom had had no such training the last two years of school. Too many were unable to swim, could not jump over a bar two feet high, or chin themselves seven times.

An analysis of defects which disqualified draftees ranging in age from eighteen to thirty-seven showed, according to Rowntree,* the following percentages of defects: manifestly disqualifying defects such as missing limbs, congenital deformities and obvious disabilities resulting from illness or injury, 10.5 per cent; mental disease, 16.6 per cent; mental deficiency, 13.8 per cent; other musculo-skeletal defects, 7.5 per cent; syphilis, 6.7 per cent; cardiovascular disorders, 6.5 per cent; hernia, 5.7 per cent; neurological defects, 5.1 per cent; defective vision, 5 per cent; hearing, 3.9 per cent, and teeth, 0.9 per cent. Overweight and underweight were together responsible for 1.5 per cent of rejections. The author calls attention to the fact that the incidence of defects per 1,000 men examined is a better index of the health and fitness of the young men of the country. Among all men examined during a six months' period, 1,583 defects per 1,000 men were recorded. Incidence rates for the chief defects appearing among these men were: eyes, 115.7 per 1,000; teeth, 140.3; cardiovascular defects, 100.4; skin defects, 115.8; defective feet, 145.0; musculo-skeletal defects, 101.3, and hernia, 64.8.

Medical science alone cannot prevent or cure many of these causes of disability. The prevention of certain inherited conditions depends on eugenics; of certain contagious diseases, on quarantine by health departments, as well as vaccination; of musculo-skeletal defects, on safety devices in industry, the home and in traffic; of syphilis, on morals and public education. Refractive errors in vision cannot be prevented, although they can be largely corrected by glasses. Hernia, which accounts for comparatively few rejections, can be corrected. Dental defects were the cause of relatively few rejections. There is room, however, for improvement, not so much in the quality but in the quantity of dental care received in our country.

So the Physical Fitness Program concerns not only physical education and medicine but all agencies concerned with the physical well-being of Americans from the cradle to the grave. These include athletics of all sorts for school children; golf, fishing, hunting and the like in which adults can participate. It includes every activity devoted to the prevention of disability through accident or disease. It involves also an educational program to inform the public of the desirability of physical fitness and health, the importance of prevention of those things which cause disability, and the possibility of correcting certain defects in the interest of greater fitness.

We have been discussing disabilities found in

*Rowntree, Leonard G.: Physical fitness for America. Hygeia, 22:744, (Oct.), 1944.

young men examined for military service. We have no similar gauge for determining the physical fitness of young women of the draft age. They are probably no more physically fit than the young men. The fitness program concerns them and also men and women beyond the draft age. It is asserted, and doubtless rightly so, that when men and women finish their schooling and enter their life work they become progressively less fit. They have less time to devote to keeping in trim and grow careless in health matters.

When a nation goes to war, physical fitness of the young men of the country is a vital matter. Fortunately or unfortunately, fitness in our modern civilization, though desirable, is not so essential. Whether a man can chin himself seven times, or jump two feet, is not so important, but maintenance of good health is important. We can recollect many examples of individuals who would be rejected for military service but have been outstanding in business, the professions and the arts. These men and women have triumphed in spite of physical disabilities.

Physical fitness is a worthy objective for the laity and the medical profession alike. Every activity that favors physical and muscular development merits support. On the other hand, man has his intellectual, moral and spiritual side in addition to his physical side. The youth movement in Germany was highly successful in developing the physical fitness of her young men and women. Lack of emphasis, however, on the moral and spiritual needs of her people has resulted in tragedy for Germany and the rest of the world.

KIDNEY DAMAGE FROM SULFONAMIDES

THAT care should be exercised in the administration of the sulfa drugs should be emphasized. Two types of damage may be caused by sulfonamides. The more common one is kidney damage caused by the precipitation of sulfonamide crystals in the renal tubules, kidney pelvis or ureters causing a reduction in urinary output which may progress to a state of anuria and even death. Less common is a toxic action of the sulfonamides on the kidneys producing oliguria, anuria, albuminuria and uremia without the usual symptoms of pain, hematuria or crystalluria. In these cases there is tubular necrosis in the kidneys and there may be focal necrosis in the liver spleen, heart and brain.

Hall and Spink* have issued a warning and have made a real contribution in an extensive review of the literature and an anlysis of twenty cases of kidney damage, some fatal, which have been encountered at the University Hospitals during the past three years.

According to the authors, kidney damage occurs in 1 to 10 per cent of individuals taking sulfonamides with no distinction as to sulfathiazole, sulfadiazine or sulfamerizine. Symptoms are most likely to appear after three or four days of medication; sooner after intravenous administration. They are more likely to occur after large doses but have been reported occasionally following small doses so that the physician should be on his guard. Even low blood concentration is no assurance that kidney damage will not occur.

It behooves the physician, therefore, to take certain precautions in the use of sulfonamides. They should not be prescribed unless indicated and the dosage should not be larger than necessary. For urinary tract infections 2 to 3 grams a day is sufficient. Even in pneumococcic pneumonia 4 to 5 grams of sulfadiazine and 2 to 3 grams of sulfamerizine daily will maintain a blood level of 8 to 10 mg. per cent in most patients, a level which is sufficient. When administering the drug, fluids should be forced so that the urinary output is at least 1,000 c.c. every twenty-four hours. Inasmuch as the drugs are more soluble in an alkaline medium, soda bicarbonate should be given at the same time in sufficient amounts to produce an alkaline urine whether it requires 4 or as high as 45 grams each twenty-four hours.

Daily urine specimens should be examined for evidence of blood or crystals. The urine should be centrifuged and examined immediately for the presence of crystals as their presence in cooled urine is not significant. Symptoms such as nausea or vomiting, rash, lumbar pain, oliguria or anuria are indications for stopping the medication and forcing liquids and soda bicarbonate. Lack of prompt response to such treatment may necessitate ureteral catheterization and lavage of the renal pelvis with warm water or soda solution.

As the authors point out, the sulfonamides have not been replaced by penicillin. They are less expensive and more efficient in the treatment especially of infections due to gram-negative or-

*Hall, Wendell H., and Spink, Wesley W.: Renal damage due to sulfonamides. Staff Meeting Bull. Hosp. Univ. of Minn., 16:75, (Nov. 10) 1944.

ganisms. Their use, however, requires certain precautions.

THE ARMY NEEDS NURSES

MISS Ruth B. Freeman, president of the Minnesota Nurses' Association, has received a communication from Major General Norman T. Kirk, Surgeon General of the Army, in which he announced that there is a critical shortage of nurses in the Army and that there has been a disappointing response to the call for 10,000 additional nurses who must be recruited within the shortest possible time.

Major General Kirk explains the need for more nurses is heightened by the fact that the Medical Department is required to activate during November and December and to ship overseas hospitals it had not expected to organize before next March. This is due, the General said, to the activity on all three fronts and the ever-increasing number of casualties which are now about 12,000 a week.

Doctors are urged not to ask private practice nurses to stay on cases longer than aboslutely necessary nor to expect extra service in the hospital. Hospital authorities are requested to make every possible adjustment and to save the strength and health of their nursing staff. If the best interests of the Armed Forces are to be served, the public must not make unnecessary demands upon nurses in or out of hospitals and must lend a hand as volunteer aides and orderlies.

Minnesota's quota for the period from July to January, 1945, is 312 nurses, and so far only 130 nurses have enlisted. A special effort must be made now to provide the nurses needed for the military campaign. Minnesota has always met its quota in the past, and we must not fail this time! Therefore, doctors and hospital administrators are being asked to reconsider their nurses' classifications and release those who are eager to go into service, if at all possible, to do so.

K.V.

CHRISTMAS SEALS

THE annual sale of Christmas seals is well under way. The sums raised in each state by the component units of the National Tuberculosis Association, of which the Minnesota Public Health Association is a part, provide the means for carrying on the fight against this still most important disease. The main function of the organization is the detection of cases and the dissemination of knowledge about tuberculosis. Sanatorium care has been provided almost entirely by tax-supported institutions.

While the mortality from tuberculosis has been reduced to about a third of what it was forty years ago when organized antituberculosis work began, tuberculosis still heads the list as the cause of death in the age group of fifteen to forty-five. Last year it claimed 56,000 victims.

Tuberculosis has increased in incidence as a result of the war. The deplorable lack of food and sanitation most in evidence in the formerly occupied areas of Europe and especially in China have resulted in increased ravages from tuberculosis.

There is every evidence that there will be a general increase in the mortality from tuberculosis in our own country in the next few years. Last year it increased 5.5 per cent in the states of New York, New Jersey, and Massachusetts. There was a slight increase even in Minnesota.

It has become more and more apparent that further reduction in the incidence of tuberculosis will depend on an extension of the Mantoux testing and x-raying of positive reactors—about 1 per cent of the half-million persons x-rayed by the United States Public Health Service in 1942-43 had significant tuberculosis. Only in this way can tuberculosis be detected early enough to be amenable to treatment. It goes without saying that there should be no letup in sanatorium care and follow-up of known tuberculous individuals.

MEDICAL ECONOMICS

Edited by the Committee on Medical Economics
of the
Minnesota State Medical Association
George Earl, M.D., Chairman

"WE ARE GOING TO STAND PAT . . ."

Columnists are predicting that the President will ask Congress for sweeping expansions of the social security system, including federal assistance for medical and hospital care, at the January session. Indeed, the President is reported as having said so at the first cabinet meeting held after the election.

Some adjustments of the social security act are generally considered as necessary and inevitable; but whether Congress is ready to accept so radical an expansion as sickness insurance is still regarded as doubtful, though the official endorsement of the Wagner-Murray-Dingell Bill by union labor is bound to carry weight, especially with Congressmen from districts where the labor vote was powerful in the last election.

In any case, the medical profession should not lose sight of the influence of labor policies upon social developments in the future. Nor of the genuine interest of labor leaders in the health of workers.

Union is on Record

As a sidelight on labor's policies, the paper read by Clayton W. Fountain, assistant to the vice president of the United Automobile Workers, CIO, at the last American Hospital Association convention, is illuminating.

As quoted in *Modern Hospital,* Mr. Fountain declared frankly, at that meeting, that UAW-CIO is on record in favor of the Wagner-Murray-Dingell Bill.

"I announce this," said Mr. Fountian, "as a matter of putting my cards on the table."

Labor is not anxious to see the state take over all social functions, he added; but in the matter of providing medical services he believes the private agencies have so far failed.

"Labor supports the bill because private agencies in the medical field are not doing a proper and adequate job of insuring health of the common people of America," he declared. "It is strictly a practical problem with us."

"Do a Better Job," Hospitals Urged

At the same time, Mr. Fountain urged his audience, composed of hospital executives and medical men, to go out and organize a better and less costly service than the government can supply.

"If you do that kind of job," he said, "you will have met the arguments for federal health insurance. Until then, we are going to stand pat on our support of the Wagner-Murray-Dingell Bill."

Mr. Fountain undoubtedly expresses the point of view of a substantial section of union labor and it is significant and encouraging that, unlike many other backers of the Wagner-Murray-Dingell Bill, he, at least, is not convinced that government can do the job better. He is interested only in achieving a generally available system of sickness insurance for workers.

In the home stronghold of UAW-CIO, medicine is already showing that voluntary insurance against costs of medical service is practical. The expansion to other states of systems comparable to Michigan Medical Service will perhaps provide the answer to labor's demands and, at the same time, protect the standards of medical service. It is obvious that the threat to high standards embodied in the invasion of government into medicine has not yet been made sufficiently real or impressive to leaders of union labor.

Meanwhile, several unions are experimenting with various types of health plans. The Health Institute established by Mr. Fountain's own organization at Detroit is one of the most recent.

Health Institute Expands

Service at the Health Institute is limited to diagnosis. For treatment, workers are referred back to their own physicians or to the company, in case of industrial accidents. In this respect it is unlikely either the Henry J. Kaiser Permanente Foundation, or the Health Center of the International Ladies' Garment Workers' Union in New York City. The institute is financed by local unions which make per capita contributions, ranging from three-fourths, to one-and-one-half cents per member per month. Nonsubscribing auto unions including some A F of L affiliates, are eligible to use the institute on a fee basis. It is reported that plans are on foot to invite such unions to participate on a per capita basis.

No plans are reported to have been made, as yet, to provide medical or hospital service; but officials have pointed out that the three-acre estate of Edsel Ford, just purchased at a cost of $51,000, would be an ideal site for a hospital.

Acting director of the Institute is Dr. Kingsley Roberts of New York's Medical Administration Service, long an advocate of prepaid group medical service.

CONSUMER EXPENDITURES FOR MEDICAL SERVICES

The Committee on Medical Economics is indebted to Dr. C. J. Potthoff of the University of Minnesota for the following analysis of recent official estimates of consumer expenditures for medicine.

Estimates of consumer expenditures for goods and services have recently been released by the Department of Commerce.† These estimates are doubtless of considerable interest to physicians concerned with economic aspects of medicine. Figures for the years 1929 through 1943 are included in the June, 1944, release.

Total consumer expenditures for goods and services in 1943 were $97,750,000,000. Of this amount $66,050,000,000 was spent for goods and $31,700,000,000 for services. Total expenditure for the same items in 1942 was $88,681,100,000.

During 1942 expenditures for medical care were $3,846,300,000. These figures do not include expenditures other than by consumers; salaries of nurses or physicians employed by government agencies, and expenditures for a city health department or a government hospital would not be considered here. The consumer expenditures were divided as follows:

Physicians	$1,094,400,000
Osteopaths	48,700,000
Chiropractors	42,200,000
Chiropodists and podiatrists	20,200,000
Dentists	540,000,000
Private duty trained nurses	59,800,000
Practical nurses and midwives	61,000,000
Miscellaneous healing and curative professions	20,800,000
Privately controlled hospitals and sanataria	628,500,000
Net payments to group hospitalization and health associations	29,700,000
Student fees for medical service	2,300,000
Accident and health insurance—net payments	163,900,000
Mutual accident and sick benefit association —net payments	32,700,000
Drug preparations and sundries	794,200,000
Ophthalmic products and orthopedic appliances	308,400,000

For comparison purposes, consumer expenditures in 1942 for selected goods and services are presented:

Food costs, including that for home consumption, estimated value of food consumed on farms, purchased meals including tips; but not including alcoholic beverages	$23,852,200,000
Housing expenditures, including rental value of rural and urban homes whether owner-occupied or not, and payments for rooms in hotels, clubs, schools, institutions	10,127,200,000
Household operation	13,294,300,000
Clothing, accessories, and jewelry	12,547,200,000
(Of the above, jewelry and watches cost $618,500,000)	
Recreation	4,639,900,000
(Of the above, $875,000,000 was spent on movies)	
Religious and welfare activities	1,232,800,000
Transportation	5,576,300,000
Tobacco products and smoking supplies	2,420,000,000
Alcoholic beverages	5,187,000,000

During 1943, according to a release of the Department of Commerce on March 22, 1944, consumer expenditures for beverage alcohol rose to more than six billion dollars or almost seven per cent of all expenditures for goods and services; the increase over 1942 was due to high unit prices rather than to increased consumption. Tobacco costs were about 2.7 per cent of consumer expenditures in 1942.

Percentage distribution of consumer expenditures are shown in Table I.

†Shaw, Wm. H.: Consumption Expenditures, 1929-43. Survey of Current Business, June, 1944.

The shifting tides of consumer expenditures since 1929 are shown in Table II.

TABLE I

Group	1929-41 average	1943 distribution
Food, alcohol, tobacco	30.2	37.4
Clothing, accessories, jewelry	12.8	15.1
Personal care	1.5	1.8
Housing	14.1	10.6
Household operation	14.5	13.6
Medical care and death expenses	4.9*	4.8
Personal business	4.0	3.0
Transportation	9.6	5.8
Recreation	5.2	5.1
Private education and research	0.9	0.9
Religious and welfare activities	1.6	1.5
Foreign travel and remittances	0.9	0.2

TABLE II

Year	Total consumer expenditures for goods and services (In millions of dollars)	Total for medical care	For physicians' services only (medical doctors)
1929	78,425.7	2,986.1	958.9
1930	71,081.1	2,893.5	923.9
1931	61,418.0	2,575.1	818.6
1932	49,672.4	2,174.2	660.7
1933	46,552.4	2,010.0	617.1
1934	51,998.3	2,200.7	678.0
1935	56,448.9	2,332.5	731.4
1936	62,272.1	2,527.0	820.4
1937	66,219.3	2,681.3	854.3
1938	63,302.8	2,690.1	832.8
1939	66,466.1	2,854.0	865.9
1940	70,806.2	3,029.8	912.8
1941	80,605.8	3,405.1	991.2
1942	88,681.1	3,846.3	1,094.4

*4.2 per cent for the various aspects of medical care and 0.7 per cent for death expenses.

NATIONAL CONFERENCE ON MEDICAL SERVICE

Postwar distribution of medical care will be the theme for the nineteenth annual session of the National Conference on Medical Service to be held in the Red Lacquer Room of the Palmer House in Chicago, Sunday, February 11, 1945.

Medical legislation, physical fitness program, rehabilitation of veterans, latest word from the Washington front, relationship between labor and farm groups and medicine are among the topics to be discussed by nationally known speakers who will appear on the program. Also listed on the program will be an open discussion on prepayment medical plans, the principal advantages and defects of both service and indemnity types of insurance being presented. Congressman Arthur L. Miller of Nebraska, author of the Miller Bill to unify certain health services, is to be among the speakers.

C. L. Palmer, M.D., Pittsburgh, is president of the conference, and W. L. Burnap, M.D., Fergus Falls, is a member of the conference executive committee.

All members of the American Medical Association are invited to attend. Programs will be ready January 1, and may be obtained by writing Cleon A. Nafe, M.D., secretary, National Conference on Medical Service, 822 Hume Mansur Building, Indianapolis 4, Indiana.

MINNESOTA STATE BOARD OF MEDICAL EXAMINERS

J. F. DuBois, M.D., Secretary

Minneapolis Quack Sentenced to One Year Workhouse Term

Re: State of Minnesota vs. Frank J. Brady, alias Frank Bateman

On October 27, 1944, Frank J. Brady, alias Frank Bateman, fifty-nine years of age, entered a plea of guilty in the District Court of Hennepin County to an information charging him with the crime of practicing healing without a basic science certificate. Brady was sentenced by the Hon. Vince A. Day, Judge of the District Court, to a term of one year in the Minneapolis Workhouse.

Brady was arrested on September 10, 1944, following a joint investigation by the Minnesota State Board of Medical Examiners and the Minneapolis Police Department. It was learned that Brady was having women come to his apartment at 3519 Emerson Avenue South, Minneapolis, under circumstances indicating that Brady had returned to the illegal practice of medicine or criminal abortion. Two women were found at the place, one of whom stated that she had paid Brady $150 for an abortion but that because of the defendant's constant intoxication he was unable to proceed with the work. The police seized various medical and surgical instruments and other equipment used in the performing of abortions, including forty-eight catheters. Brady's case was continued several times and on one occasion he failed to appear in Court. Judge Day forfeited Brady's bond and issued a bench warrant for his arrest. Upon being brought into Court, Judge Day increased Brady's bond to $3,000 from $1,000, the amount originally set.

Brady has a long criminal record dating back to 1922, when he was convicted of grand larceny in the second degree at Saint Paul, for which he served thirty-one months in prison. In October, 1931, under the name of Frank Bateman, he pleaded guilty to a manslaughter indictment in Minneapolis, following the death of a woman from criminal abortion. Brady served six years for that offense. In July, 1941, Brady was sentenced to serve one year in the Minneapolis Workhouse for practicing healing without a basic science certificate. He claims to be a bartender by occupation.

Minnesota Academy of Medicine

Meeting of May 10, 1944

The regular monthly meeting of the Minnesota Academy of Medicine was held at the Minnesota Club, Saint Paul, on Wednesday evening, May 10, 1944. Dinner was served at 7 o'clock and the meeting was called to order at 8:15 by the President, Dr. Walter Camp.

There were forty-seven members and three guests present.

Minutes of the April meeting were read and approved.

Dr. A. R. Colvin read the following Memorial to Dr. Arnold Schwyzer and a motion was carried that this be published in the Proceedings of the Academy and a copy sent to Dr. Schwyzer's family.

ARNOLD SCHWYZER, M.D.
1864—1944

Dr. Schwyzer was born in Zurich, Switzerland, in 1864. After six years in college, he undertook the study of medicine, graduating at the University of Zurich in 1888. He served one year as assistant in the County Hospital at Glarus, and for a short time as assistant in the Surgical Clinic of Korenlein, and finally three years at the obstetrical and gynecological clinic at the University of Zurich.

During a visit to Edinburgh, he met the American Consul to whom he presented a letter of introduction from a prominent St. Paul citizen, a friend of his family who had lived with them in Switzerland during his college term. The American Consul, knowing of his intentions to come to the United States, advised him to come as a highly-trained surgeon else he would just become another doctor. The soundness of this advice is evident even today. In those days, numbers of American doctors embarked upon journeys of study in the older centers of medical education in Europe, to round out their training. His was the advantage of being taught by great teachers and of being associated with them in hospital work during his formative years. The inspirations derived from early association with great men in medicine cannot be overestimated.

Because of these advantages, he was at once recognized and generously acknowledged by a group of men in Saint Paul, who, although lacking laboratory training and experience, were men of great spirit and high ideals, sound clinicians, and fine surgical capacity and judgment. Dr. Schwyzer soon recognized this and became a peer among a group of men who had become nationally known for their outstanding spirit of ethics, kindliness and helpfulness to young men.

The recognition thus early obtained soon extended over a much wider area than his own locality. He became a member of (1) The American Surgical Association, (2) American College of Surgeons, in which he belonged to the founders' group, (3) Minnesota Academy of Medicine, (4) Western Surgical Association, (5) American Medical Association, (6) Minnesota State Medical Association, (7) Minnesota Pathological Society, (8) Ramsey County Medical Society, and (9) Swiss Surgical Society.

He was awarded the medal of the Minnesota Academy of Medicine in 1929, the first and only medal given for outstanding contributions to the organization.

He early acquired a large surgical practice which continued to grow year by year. He was an indefatigable worker. His daily routine began at the hospital at 7:00 a.m. He was an individualist in his work—and entitled to be this—and the fact that he was possessed of a great sense of responsibility for his patients accounts in part for the fact that he employed only one assistant in his large volume of surgical work, and never in any sense developed the group or clinic idea. He thus, naturally, held in a marked degree the confidence and admiration of his patients.

He was his own internist, pathologist, chemist, radiologist, physicist, and radiographer. This enormous amount of work increasing in volume from year to year could only have been carried on, practically alone, by a man of unusual physique endowed with great intellectual power, and these he devoted more and more as the years went by to the application of an increasing knowledge of medical science to the needs of his patients, and this went on day by day, year in and year out.

In the meantime he kept abreast of medical progress by continuous study, emphasizing Dr. Osler's epigram that the master word in medicine is work. When unusual cases presented themselves and were discussed among hospital men, he was always prepared with the ancient and recent knowledge of the subject and, being accused of looking up the information the night before, he said, "Do they think I just know; they do not know how hard I work to acquire all I know." Men of his calibre are not jealous of others, but they no doubt challenge supremacy and usually have it. It was fine to see how his contemporaries acknowledged it. Such men engaged in private competitive practice are always under close scrutiny, but if his colleagues found any flaws in him, they overlooked them. He was intrinsically one of them and a good fellow. Such is foundationally the character of medical practitioners.

Perhaps all men of his size feel the sporting instinct of leaders. A very innocent evidence of it in him was disclosed in his equestrian excursions. These early morning rides started out as very proper and dignified performances, and, although he could ride hard, the commander's order was that there should be no racing. However, let the other's horses nose ahead a little —as will happen in western horses—the race was on,

and the sedate and dignified canter became a furious gallop.

In his play—all the way from checkers, cards, or what not—he put all he had into it as he did in his work. His busy life left little time for social affairs even if he was a very socially-minded man. However all during his working life—and that was until the last month— he made numerous vacation trips to his beloved Switzerland, taking his entire family with him. While these were vacations, he nevertheless kept in touch with what was going on in medicine, made easy by his many friends in university and hospital circles.

The years that he did not go abroad, he spent two or three months each on his large farm situated on the shores of Grindstone Lake in Pine County. This large tract of land he converted from a mostly burnt-over, wild country into a productive and picturesque spot with bridle paths through the woods where he loved to ride with his guests and discuss agricultural projects on which, by the way, he kept as well informed as he was in medicine, he and his brother, Gustav, being frequent visitors to the Agricultural College.

During their summer vacations on the farm, Dr. and Mrs. Schwyzer were rarely without guests, the entertainment of whom gave them continuous pleasure. In a separate study built over the edge of the lake, Dr. Schwyzer nevertheless caught up with medical literature not only in medical journals, which in his hard-working months he had not had time to read, but the reading of some advanced work on physics or chemistry was also saved for this period. He had an amazing memory for the complicated formulae of organic chemistry.

His essay on "Musings on Excerpts on the Origin of Life" was published in phamphlet form that his friends, of whom he had many, might receive copies as a greeting and a sign he should have liked to have their discussion while pondering over these problems. These "Musings" were a summarizing analysis of what the natural sciences have to offer for a conception of an origin of the organized world from the inorganic. This study had its origin in a sheer love of an almost oriental abstract contemplation. Only a mind informed in chemistry, physics, embryology, geology, et cetera, could be more capable of the "Musings" found in this pamphlet, and so this active mind was unceasingly at work even in holiday times, and, if his guests were at all like-minded, he kept them busy listening to a recital of all he had been reading during his holiday.

He enjoyed the company of his fellows and while on his broad acres at the lake in Pine County, he was the squire of the district, acquainted with the farmers of his neighborhood and all their problems and difficulties. His many loans were not investments that brought him many returns.

He found time, during his many years of an unusually large and exacting practice, to write 108 articles. These covered a large part of the field of general surgery and most of the surgical specialties were largely subjects related to his surgical practice, and of a reflective, analytical and investigative nature. Notable were, early in his career, his report of an operation and cure of subclavian aneurysm, resection of the femur in continuity for sarcoma with transplantation of the fibula; both of these patients were presented at medical society meetings many years afterwards.

He originated a plastic operation on the pelvis of the kidney for hydronephrosis due to obstruction of the pelvo-ureteral junction which has become a standardized procedure.

He was an optimist in both medical and surgical therapeutics. An article entitled "Defeatism in the Treatment of Malignancy" reflected this characteristic. In the years when surgery was making great advances, he was in the front lines of the advance. His inaugural Thesis for this Academy in 1894 was on the "Infectious Nature of Carcinoma. Inoculation of Cancer in the Wound Made for Total Extirpation of the Cancerous Womb." His last paper before this group was on "White Bile." In the interim he had read fifty-three papers and numerous case reports. His numerous discussions of papers read were not confined to surgical subjects.

His was the value of a highly intellectual and practical surgeon, experienced from years of keen, thoughtful observation, endowed with the faculty of evaluation, being self-reliant and possessed of high ideals and integrity and singleness of purpose. All these are required in the suddenly changing scenes of action in the successful surgeon. It goes without saying that the character of his work, and the manner of life he led, exerted a profound influence on his community.

That he was imbued with a desire to teach is evidenced by the fact that he was Professor of Pathology at Hamline University from 1900-1902 and, during this period, pathologist to the City and County Hospital. From 1904-1908, he was professor of Clinical Surgery at Hamline University. In 1927, he was appointed Professorial Lecturer at the University of Minnesota, and in 1932 was made Professorial Lecturer Emeritus. Too late in life he was offered the Chair of Surgery at the University of Minnesota. Having by this time become involved in a very large surgical practice, he decided that at this time of life he could not carry the double load, and he was so constituted that he would not undertake anything that he could not give all the time and effort required to make it a success. It was a great pity that the opportunity did not come to him earlier that he might have developed and organized his efforts as a great teacher and thus have widened his influence in his community. However, in his well-organized one-man unit, both by example and precept, his influence was felt in his hospital work by succeeding groups of interns and by many visiting physicians.

He was a wonderful mathematician. He was born in 1864, and said in 1934 that the difference between 1864 and 1934 was fifty-five not seventy. The period from 1934 to 1944 would be ten years and he should be eighty, but I am sure you will all admit that as far as mental activity was concerned he was one of the youngest members of the Academy.

The last year of his life ran true to form. He had been having abdominal distress for a year but, not

wanting to cause any uneasiness in others, did not mention his illness to either family or friends until a few days before an exploratory laparotomy was done. He performed a major abdominal operation the day before his own, had one scheduled the same day as his own, and then suddenly decided to surrender. After that, he was the same self-reliant man, knowing his fate, discussed it at times briefly, predicted the date, said it was hard waiting, but he could take it. The impatient man became patient and hoped he would not be impatient, and left believing that the universe could not go wrong. These last days were an inspiration and long to be remembered.

The scientific program followed.

CARCINOMA OF THE TOE AND METASTASIS
Report of a Case

A. E. BENJAMIN, M.D.
Minneapolis

F. J., a man aged forty-nine, first consulted me March 1, 1940, on account of pain in the upper left abdomen. The trouble began in 1938. He improved for a time under treatment but of late had been suffering considerably. He also complained of some impaired vision.

His father had died at seventy-two, his mother at twenty-eight from infection at child birth. One brother was living and well. One sister died at fifty. He had had no children. He gave a history of having an operation for hernia in 1924 and a tonsillectomy in 1939.

He was five feet eleven inches tall, weighed 170 pounds, his blood pressure was 120/80. His abdomen was distended, especially in the upper left quadrant. The urine contained a trace of albumen.

An x-ray showed moderate gastritis and a diverticulum of the third portion of the duodenum.

With dietetic management, he gradually improved so that in about a month's time he was comparatively well and complained of no pain in his abdomen.

I did not hear from him again until October 27, 1943. He then stated that he had had a great deal of pain in his head for two months. He was exceedingly nervous and could not sleep. He consulted various doctors, including a chiropractor and took several electrical treatments. The diagnosis made by a number of doctors was sinusitis. He stated that he had taken a great deal of medicine to stop the pain and to make him sleep. The pain was greatest at this time through and near the left eye and nose.

An x-ray taken in August, 1943, showed a bilateral sclerosing mastoiditis of long standing and a right frontal and ethmoidal chronic sinusitis. His pulse remained between 80 and 85. His frontal sinuses were tender to percussion. There was some soreness on pressure over the stomach and colon and these were somewhat distended.

He had an ingrowing toe nail on his left big toe. It had never healed after an operation done elsewhere, about three weeks previously. There was some enlargement of the inguinal glands.

He was sent to the Northwestern Hospital for observation and treatment October 27, 1943. On October 30, the unhealed area on the big toe was excised. The pathologist reported a squamous cell carcinoma.

An x-ray of the stomach on November 1, 1943, demonstrated a delay in emptying after four hours. The x-ray of the lungs showed a probable malignant infiltration of the right lung.

On November 4, Dr. Ulrich, in consultation, reported he was of the opinion that there was a metastatic carcinoma of the lung and also of the brain.

On November 6, Dr. Gammel examined the patient. He was of the opinion, on account of the pain in the eye, that the headaches were of a migraine nature.

Dr. Phelps, on November 6, made a bronchoscopic examination and reported no evidence of obstruction of the bronchi and was unable to observe any area that might be carcinomatous.

The blood picture and spinal fluid examination on November 4 were normal.

The patient went home on November 21 but returned to the hospital December 20 because of nervousness, sleeplessness and weakness.

Dr. Gammel re-examined the patient on November 21 and found the eyes in all respects virtually normal.

Dr. Michael saw him in consultation, and on December 22 an encephalogram was decided upon. Ten c.c. of the spinal fluid was slowly removed and replaced with 10 c.c. of air and the procedure repeated until 110 c.c. of fluid had been removed and 100 c.c. of air injected. An x-ray of the brain was then taken. No brain lesion or abnormality was found.

After the encephalogram was taken, the patient's temperature went up to 101 the next day and gradually declined to normal so that on the last of December, he had no fever and his pulse rate was normal.

His toe continued to bother him. His headaches began to return and his right knee started to pain a great deal so that morphine had to be given occasionally for relief. Heat and aspirin gave him some comfort during the day but on account of pain and sleeplessness sedatives had to be given at night. The toe showed no signs of healing, and the glands in the groin began to enlarge. The glands were removed for biopsy and relief. They were found to be malignant. A few days later the toe was amputated.

An x-ray was taken of the right knee but showed no lesions. Another x-ray was taken of the lung and this showed more definite signs of malignancy.

The patient remained in the hospital until February 7, 1944, when he returned home. He slowly declined and died suddenly on April 24, 1944, at 6:45 A.M.

A postmortem was held but unfortunately the skull was not opened. The report was as follows:

The heart weighed 400 grams and the myocardium showed scattered fibrosis. The coronaries were slightly sclerotic but showed no narrowing. The right lung weighed 1150 and left lung 1250 grams. They were markedly emphysematous and edematous. The right upper lobe contained a firm whitish area about 8 cm. in diameter arising from the right upper lobe bronchus and not quite reaching the periphery. Some pus could be expressed from this area. The spleen weighed 150 grams and was somewhat fibrotic. The liver weighed 2000. There was a diffuse whitish infiltration scattered about and also many discrete nodules, white and firm, ranging from one to 6-7 cm. in size. The right adrenal gland showed one large white hard nodule about 2 cm. in diameter and several smaller ones. The left adrenal showed some very small nodules. The right kidney weighed 225 gms. and the left 250. They showed no gross pathology. The other organs were normal.

The tumor in all the organs consisted of nests of squamous epithelial cells. There was no definite keratinization, which speaks for its origin from the bronchus instead of the skin. Its location in the lung is also in favor of this origin. There were many areas of necrosis in the tumor in all its locations. In the lung, there was some polymorphonuclear reaction in the areas of necrosis, significant of some superimposed

infection. Around the tumor, the nontumor-containing lung was full of very large macrophages with phagocytosed blood pigment and fat globules. The liver and adrenals showed similar tumor nodules. None was found in kidneys, spleen or pancreas. The kidneys showed some tubular atrophy.

Diagnosis:—Squamous cell carcinoma of bronchus with metastases to skin, adrenals and liver.

I have asked Dr. Cy Hanson to describe the x-rays and Dr. Michael to give the neurological interpretations of the symptoms. Dr. Phelps will explain his bronchoscopic findings.

I do not think we can say where the primary growth was. The postmortem findings would indicate it was in the bronchus but the first known tissue affected was the left big toe.

Discussion

DR. KENNETH PHELPS, Minneapolis: This man presented the x-ray finding of a shadow in the right upper lobe of his lung without any clinical evidence of chest disease. Usually a primary carcinoma of the brunchus produces some symptoms. For example, cough is present in about 100 per cent of them. This man had no cough, no pain, and no blood-streaked sputum. The only reason for bronchoscopy was the x-ray finding of a mass. I could find no visible evidence of tumor. When I heard later that carcinoma had subsequently been found in the toe and glands of the groin, I thought this was metastatic and not primary carcinoma of the lung.

DR. J. M. MICHAEL (by invitation), Minneapolis: I saw this man first on December 10. At that time the most prominent complaint was headache day and night, persistent since last August. He also had the complaints of a melancholic, he was greatly worried, he was blue, his wife worked and then went out to the pool halls, not coming home before 2 a.m., which worried him a great deal. After I got through with my examination, and was unable to get any sign of nervous system involvement, he said: "Now my headache is gone." We naturally felt a little bit dubious at the moment about the presence of an organic brain lesion in spite of the head complaint. Several weeks later he reported his headaches came back again and at that time I was able to make out a few objective signs. The abdominal reflexes were gone and Gordon great toe extension was positive. We did a spinal air injection at Northwestern Hospital. The plates you saw were negative. After this procedure he became delirious, which I thought might represent a bromide psychosis. We had a blood bromide determination done, which was found to be 196 mgm. per cent. We put him on heavy salt administration and the delirium left him promptly. We had hoped after his death to get confirming evidence at postmortem, but unfortunately necropsy did not include the head.

DR. S. E. SWEITZER, Minneapolis: This looks to me like a comedy of errors. If the man had carcinoma on the toe first, then he had metastases in the lung and brain. If he had a primary in the lung he would have passed away sooner.

DR. J. S. ABBOTT (by invitation), St. Paul: In September, 1941, I was called in to see an elderly woman of 74 who had an ulcer on her great toe which she had had for four or five months. She had a definite cardiac disturbance with a murmur and hypertension, and the ulcer had been treated for some time with no evidence of healing. The toe was amputated at the phalangeal metatarsal joint and was reported to be squamous cell carcinoma. Some six months later she developed hemiplegia. She lived for about one and a half years after the hemiplegia. About six months prior to her death the glands in her groin enlarged, increasing to a mass about the size of a grapefruit. There was no evidence of further metastases. She died a cardiac death along with gradually failing from hemiplegia.

The question of removing glands in the groin for carcinoma of the toe has often been given considerable consideration. When we have carcinoma of the toe or hand there are so many lymph drainage channels, as in the popliteal and epitrochlear regions, reaching the groin or axilla, that one wonders whether it is advisable to go ahead and take out the glands proximal to them. I think, for these cases of carcinoma of the toe, it is a question whether it is advisable to remove the glands in the groin. I have had two other malignancies of the extremities recently. One was a melanoma on the back of the hand in a woman 80 years old. I excised it and did a skin graft. In very old people these do not recur so quickly and she hasn't yet had any recurrence. The other was a man of 72 with epithelioma on the back of the hand. This was also removed locally.

DR. A. E. BENJAMIN, in closing: In this case they were enlarged and out of curiosity and to relieve him of the pressure, I removed the glands and found a squamous cell carcinoma also.

The first symptom he complained of was in the toe, then in the groin, then the head. But the lung was never troublesome. He never coughed up any blood. We could find no rales in the lung. Dr. Ulrich looked him over pretty thoroughly. It was only because of the x-ray findings in the lung that we had the bronchoscopic examination.

I was not present at the postmortem. I thought they would surely open the skull because of the symptoms but, for some reason, they did not open the skull.

REGIONAL ILEITIS

Report of a Case

E. A. REGNIER, M.D.,
Minneapolis

This case is reported because it typifies the usual course of the disease from its early acute phase to the chronic.

Regional ileitis as described by Crohn in 1932 is a chronic inflammatory process commonly involving the terminal portion of the ileum although other parts of the small bowel may be involved. The etiology is unknown but many investigators think a virus may be the causative agent. The disease is destructive, progressive and proliferative and results in marked thickening and fibrosis of the intestinal wall, often resulting in obstruction. The symptoms early are: malaise, low grade fever, peritoneal irritation, often resembling appendicitis. In about 50 per cent of reported cases, appendectomies have been done. This phase courses into one of colic, diarrhea suggestive of ulcerative enteritis but never accompanied by melena. As chronicity progresses, obstructive symtoms predominate and finally abscesses and fistulae appear. Lahey reports 25 per cent of their cases showed fistulae or abscesses. The diagnosis can usually be confirmed by x-ray. A barium enema will often show a cord-like filling of the terminal ileum,

the lumen of which appears almost closed. This was described as the string sign by Crohn.

A married woman, aged twenty-five, had a negative past history except for appendectomy. Eighteen months previously she was treated for salpingitis (probably early acute ileitis). Eight months previously she was hospitalized on two occasions for fever, abdominal pain and diarrhea. (Second stage of the disease.)

At operation Dr. La Vake noted marked induration of the terminal ileum, cecum and colon. This was not disturbed. Pain, colic and fever, and nausea persisted. X-ray of the colon revealed no abnormality of the right colon. It was impossible to fill the terminal ileum by this method and, because of the obstructive symptoms, no barium was given by mouth. The above symptoms continued until early in April. The patient was observed, given several blood transfusions, and on April 10 an exploratory operation was done because of the presence of a large mass in the right lower abdomen. The patient had noticed this mass two months previously and stated that it had been gradually growing. On opening the abdominal wall, an abscess was encountered beneath the right rectus muscle which contained one-half ounce of thick, creamy pus. There was a very small fistulous opening leading to the base of the cecum. Upon exploring the abdomen, the mass which had been felt appeared to be a mass in the cecum proper. The terminal ileum was dilated for a distance of seven feet. The ileum was dull gray. The colon wall was edematous and markedly thickened. There was an area about 8 cm. long in the region of ileocecal valve which was very hard and the cecum was adherent to the parietal peritoneum. There were large nodes in the mesenteries of the ileum and ascending colon. Because of the obstructive lesion and because of the large nodes, I felt that we were probably dealing with a granulomatous lesion of the cecum and felt that a radical removal, together with the nodes of the mesenteries, would be most apt to give permanent relief. Fifteen inches of the terminal ileum and the entire right half of the colon were resected and an end-to-end anastomosis was done between the terminal ileum and the mid transverse colon. The diameter of the terminal ileum was greater than that of the transverse colon.

Convalescence was most uneventful. She left the hospital on the fifteenth postoperative day.

Pathological Report: The terminal eight to ten inches of the ileum was involved in an inflammatory mass. There was marked thickening of the wall of the bowel, a great deal of fibrosis, superficial ulceration of the mucosa and the lumen was one-half a centimeter in diameter. Pathological diagnosis: Terminal ileitis. (Colored slides of the pathological specimens were shown.)

There are many points of view recorded on the treatment of regional ileitis. We feel that in the acute and subacute stages medical treatment is probably best. In the event that this lesion is accidentally noted at operation in its acute or subacute stage, it is probably best to leave it alone or to do a short circuiting operation, transplanting the terminal ileum into the mid-transverse colon. On an attempted resection in the chronic stage where a good deal of cicatrix has formed in the bowel and where there is evidence of obstruction or fistulae formation, it is best to do a radical operation removing the affected nodes and mesenteries of both ileum and ascending colon.

Discussion

Dr. R. T. La Vake, Minneapolis: This case and another, quite similar, have been very interesting to me. Both, after a long period of illness associated with diarrhea and abdominal pain, were diagnosed as having a pelvic condition. The patient reported here had been hospitalized for months with a diagnosis of bilateral salpingitis, and the other came to my attention with the diagnosis of rapidly-growing malignancy of the right ovary. At operation, in one, the tubes were found to be normal and in the other the right ovary was found to be normal. To me, the valuable sign of the true nature of the right adnexal mass was the gurgling elicited in a bimanual examination, very similar to the gurgling elicited in a cecum mobile.

Both patients developed signs of obstruction necessitating operation and resection of the lower ileum. The operations were long and very difficult in the presence of much inflammation. Yet the operative reaction in each case was relatively mild. However, one may disagree with the medical treatment and watchful waiting in these two cases; at least it is possible that time and conservative treatment had built up a resistance that allowed the patient to sustain an obvious spill of pus with comparative impunity. Such spill was unavoidable with the best operative technique.

ANGIOID STREAKS IN THE RETINA
Report of a Case

ERLING W. HANSEN, M.D.
Minneapolis

This woman was a teacher, thirty-four years old, referred by Dr. Rusten who sent the following note:

"I first saw her on April 5, 1944, and my diagnosis was a pseudoxanthoma elasticum. The patient stated that the first eruption appeared at the site of the neck at the age of seventeen. This was symmetrical and yellow in color. Since that time lesions have developed over the chest and axillary folds. Over this same period of time she has had generalized pruritus, and during the past four months has had an urticarial eruption. An examination of the skin revealed an eruption at the sides of the neck, over the chest, axilla and arms. This consisted of very lax skin with yellow discolorations and being made up of pin-head to match-head sized papules, linear arrangement and also some of them causing striations. There was no history of any other member of the family having a skin eruption similar to this."

(Slides of fundus photographs of both eyes were shown.)

The retina in the right eye shows a generally mottled appearance. Around the optic disc is a somewhat irregular incomplete dark ring with brownish red lines radiating from it. For the most part they follow the general direction of the vessels of the retina but can be seen to lie at a deeper level. In some places they form more of a criss-cross network. There are three small hemorrhages in the retina and in two places small areas of exudate.

The left eye shows a much more marked network of brown lines, especially heavy on the temporal side of the disc, extending upward and downward parallel to the superior and inferior vessels. The macula appears more prominent than usual with somewhat of the appearance of cherry red spot. The pigment disturbance throughout the fundus is quite marked. There are also several hemorrhages and exudative spots in this eye.

There has as yet been no visual disturbance in this case. In some, as time goes on, there is deterioration of vision, especially marked, of course, when the macular area becomes involved.

Angioid streaks may not be too rare a condition, but

certainly it is not very common. The question of etiology of these streaks has been rather a moot question until 1929 when Grönblad pointed out association with pseudoxanthoma elasticum. In 1939 Hagadoorn found histologically, thickening of Bruch's membrane, with ruptures; thickening of arterial walls of the choroid and a disappearance of elastic tissue. Degeneration of elastic tissue elements of Bruch's membrane had been suggested in 1917 by Kofler. The largest number are in the middle-age group and probably 40 per cent of patients are over forty. It does occur in senile elastosis and has been reported also in Paget's disease. The greatest number we now know are associated with pseudoxanthoma elasticum. The streaks are caused by the breaks in Bruch's membrane.

Discussion

DR. F. E. BURCH, St. Paul: I think these cases are of interest to the dermatologists as well as to the ophthalmologists. In 1929, in Copenhagen, when Dr. Grönblad was doing her great work on association of angioid streaks and pseudoxanthoma elasticum, I was asked if I had seen these streaks often in cases of xanthoma elasticum. I did not know what she was talking about as I had never recognized a case of the latter.

The chief interest in this whole subject is the *relationship* between the skin condition and the retinal findings. Fifty per cent at least of these cases develop marked impairment of vision from central degeneration.

In regard to the etiology, these pseudo-circulatory streaks are undoubtedly blood pigment and I think the photograph I will show illustrates this deeper pigmentation. The patient was thirty-six years of age. The picture shows they have nothing to do with the retinal circulation and are not a part of the choroidal circulation. How they occur and why they occur has been a cause of a lot of theorizing and controversy—whether or not there is elastic tissue in the membrane of Bruch—but it seems to be a proper hypothesis. These patients suffer a large degree of impairment of vision. I will project a fundus picture showing the degeneration in the macula of this patient which is quite extreme.

FROM THE AUDIENCE: If you do not see the skin in the individual, how would you know that it was not a pre-senile condition?

DR. BURCH: By its association with pseudoxanthoma elasticum.

DR. S. E. SWEITZER, Minneapolis: I have had only one case of pseudoxanthoma elasticum, and in that one the eye findings were negative. I think in a fair percentage of cases reported they do have streaks. It is usually discovered in young people. My case was a teen-age youth.

The meeting adjourned.

ERLING HANSEN, M.D.
Secretary

Meeting of October 11, 1944

The regular monthly meeting of the Minnesota Academy of Medicine was held at the Town and Country Club, on Wednesday evening, October 11, 1944. Dinner was served at 7 o'clock and the meeting was called to order at 8:15 by the vice president, Dr. A. G. Schulze.

There were fifty members present.

The secretary being absent, Dr. Shulze also read the minutes of the May meeting and they were approved as read.

The scientific program followed.

ULCERATIVE HODGKIN'S DISEASE
The Value of Node Imprints in Diagnosis

S. E. SWEITZER, M.D.
Minneapolis

Dr. Sweitzer gave a lantern slide talk on the above subject. This paper will be published later in the *Archives of Dermatology and Syphilology.*

Discussion

DR. H. E. MICHELSON, Minneapolis: Dr. Sweitzer has related to you the history and findings of a very interesting case that can be discussed under three headings:

1. Clinical: There was nothing in the morphology that suggested the final diagnosis.

2. Histologic examination by the old methods made it impossible to definitely identify the preparation as one of Hodgkin's disease. As you know, we have become so accustomed to looking at fixed and stained tissue that we have no clear-cut conception of just what a cell looks like.

3. The third method of examination was that introduced to dermatology by Drs. Sweitzer and Winer. Here there is an effort made to get the free cells from pressing the cut gland against a slide and examining the preparation fresh and stained. This method offers much promise, and we hope that eventually we will be able to identify the various lymphoblastomas.

STUDIES ON EXPERIMENTAL CANCER

MAURICE B. VISSCHER, M.D.
Minneapolis

Dr. Visscher, of the Department of Physiology, University of Minnesota, gave a paper on the above subject and illustrated it with numerous lantern slides and charts.

Abstract

My purpose in this presentation is twofold. First I want to outline the basis on which cancer research is being carried out in the University of Minnesota and second I wish to tell you about some of the results of that work.

The main lines of cancer research at Minnesota are under the direction of Dr. J. J. Bittner, who is the George Chase Christian Professor of Cancer Biology. With him are associated Dr. C. P. Oliver, Director of the Dight Foundation for Genetics, Dr. R. G. Green, Professor of Bacteriology, Miss Zelda B. Ball, Cancer

Biologist, Dr. C. P. Barnum, Instructor in Physiological Chemistry, Dr. J. T. King, Associate Professor of Physiology, and your speaker, among others. This work at Minnesota is the direct result of interest by Mrs. Christian, the Citizens Aid Society of Minneapolis, Dr. Ivar Sivertsen, Mr. N. C. Beim, Mr. J. F. Bell and other public-spirited citizens, besides a large group of medical scientists in the University and in the State at large.

The work is supported partly by private gifts and partly by a special State Legislative Appropriation. The two together result in more than twenty-five thousand dollars a year being available specifically for cancer research. This sum is expended in accordance with the terms of the special gifts and under the administration of a special committee in charge of the larger sums.

Dr. Bittner has under study thirteen specially inbred strains of mice of characteristics valuable to cancer research. In all more than twenty-five thousand animals per year are studied in connection with cancer studies at Minnesota. Some of the mouse strains have been inbred under Dr. Bittner's supervision for more than fifteen years, representing fifty or more generations.

The essential element of the cancer research plan at Minnesota is one of what may be called inter-science co-operation. A fundamental cancer biologist is actively co-operating with a virologist, an endocrinologist, a chemist, a pathologist, a histologist, a tissue culture expert, a human genetics expert, a nutrionist and with clinicians, in the attack on this problem. He has the help of experts whose combined salaries would amount to twice the cost of the cancer program proper. Thus because these experts can each give part time to this work the University can accomplish a much more significant program than would be possible if the work were done in an isolated self-contained unit. It must be obvious that this is an especially economical way of accomplishing research requiring collaboration of experts in various fields. What is now essential is assurance of longer-term support for the whole project.

What has come out of this work, and what is now under way? The main studies have been and are now in the field of mammary cancer. This trend results from the fact that Dr. Bittner discovered, ten years ago, the importance of an agent transmitted from mother to young in nursing, this agent being one of the absolute essentials to high breast cancer incidence in mice.

Minnesota studies with the ultracentrifuge were the first to show that this agent is sedimented as one would expect viruses to be. The agent has been found to be filterable, sensitive to heat at 60°C. for one hour, is destroyed by weak acid, is not destroyed by extraction with fat solvents. It has, in fact, every property consistent with the view that it is a virus.

Some current studies are aimed at further chemical purification and identification of the agent. Others are aimed at attempts to potentiate and attenuate the agent, and to develop immunity to it.

One important current problem is a comprehensive survey of human breast cancer in an attempt to find evidence for or against genetic, endocrine and virus factors in its causation. This study was under way for a year before the nation-wide council on this problem was called by Dr. C. C. Little in Bar Harbor, Maine. The Minnesota studies will become a part of the national program.

Another angle of the breast cancer problem which has received intensive study at Minnesota is the influence of diet. Here it was first shown that simple restriction of caloric intake, all other factors being held constant, greatly reduces mouse mammary cancer. These studies have had very interesting and important physiological by-products. They have shown that the endocrine and sexual apparatus are altered in very specific ways by calorie-restriction. To be specific the estrus cycle is stopped or slowed, fertility is reduced or abolished, uteri do not develop beyond the pre-pubertal stage, mammae do not develop to maturity. And most interesting of all perhaps, after calorie-restriction for two-thirds the normal life span, feeding a normal diet again restores fertility, at a time when a normally fed animal has become sterile from old age. Thus caloric restriction postponed senility in these animals.

I have described only a fraction of the work that has been done by the Minnesota cancer research group and I want to emphasize again that the work is largely that of others than myself. If I have been useful it has been mainly in arranging for co-operation and suggesting some physiological approaches to the problem. Cancer is responsible for about 20 per cent of autopsied deaths over one year of age in Minnesota, according to Berman. It is surely worth our while to obtain every bit of information about it that we can. Cancer is a disease of living, growing cells and it is obvious that every branch of biological knowledge must be brought to bear on its study if we hope for success. That is what we are trying to do at the University of Minnesota and we hope that we will have your intellectual, moral and physical support in carrying it out.

Discussion

DR. C. B. DRAKE, Saint Paul: Do mice develop cancer of the ovary, or is it anywhere?

DR. VISSCHER: I talked entirely about the mammary cancer tonight.

DR. DRAKE: Was the restriction of diet the factor that caused them not to become pregnant?

DR. VISSCHER: We think that the dietary restriction inhibits the anterior lobe of the pituitary and that the inhibition of the anterior lobe of the pituitary prevents normal ovarian function. The ovarian hypofuncton prevents breast development. One of our reasons for believing this is that if you administer pituitary hormone, antuitrin-S, these animals show a normal estrus cycle and there is some mammary development.

DR. H. B. ZIMMERMANN, Saint Paul: If you break that chain by castration, does it affect cancer incidence?

DR. VISSCHER: Castration in the A strain of mice does not influence cancer incidence in virgins because the virgins are low cancer anyhow. In the C 3 H strain a very interesting thing happens—instead of having a zero cancer incidence one has a very high cancer incidence in castrated animals, but it is delayed. It is at 16 to 18 months instead of 10 to 14 months and it only occurs after adrenal cortical tumors develop. Not

(Turn to Page 1038)

simple depression

"...the most favorable of all disorders for benzedrine therapy."*

In simple depression, Benzedrine Sulfate therapy may be expected to benefit the patient by breaking the strangle-hold of pathologically organized habit-patterns and by restoring what Myerson calls the patient's "energy feeling".

The following instances of simple depression are familiar to every physician:—

1. Depression following acute infectious disease, typically influenza.

2. Depression following surgical operations.

3. Depression following pregnancy and childbirth.

4. Depression accompanying the onset and course of the menopause in women and the involution period in men.

5. Depression associated with menstrual dysfunction.

6. Reactive depression precipitated by an external problem situation which the patient can neither resolve, tolerate, nor ignore.

*Guttmann, E. and Sargant, W.—B. M. J., 1:1013, 1937

BENZEDRINE
SULFATE TABLETS
(RACEMIC AMPHETAMINE SULFATE)

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only do they develop cancer, but they go into continuous estrus and there is abnormal breast development. By removal of the ovaries, one upsets the endocrine balance so that the adrenals take over a function they did not have before.

DR. H. L. ULRICH, Minneapolis: What is the milk agent? A virus?

DR. VISSCHER: The milk agent has to be present before the mouse has produced a litter. The interpretation that has been given is that the virus has to be present while there is rapid proliferation under hormonal influence in order to set the stage for mammary cancer. The virus is in the mouse from the day of birth to the time of cancer development.

DR. ZIMMERMANN: If you have a little brother and sister both of whom have received the milk factor from the mother and then you take a mouse that has been taken away from the mother and foster fed, is this milk factor in the blood serum of the mother, and can it be transferred by transfusion?

DR. VISSCHER: Yes, that has been done; the agent is present in the blood.

DR. R. T. LA VAKE, Minneapolis: Experimental work on animals seems to point to the following conclusions: that cancer is influenced by heredity, that nursing from a cancer strain mother increases the chance of cancer in the offspring, and that estrin, at least, stimulates cancer growth. These findings translated into practice suggest the advisability of especial watchfulness when cancer is in the history: not permitting such mothers to nurse their babies; and not giving such women estrin for menopausal symptoms. May I add that the annoying symptoms of menopause can be adequately handled without the use of estrin. It is possible that the lowering of estrin production is a beneficent action on the part of nature at this age. The amounts of estrin being given for menopausal symptoms is tremendous. I would like to ask Dr. Visscher if he believes that harm may be done by such treatment.

DR. VISSCHER: Yes there is a chance that estrogen administration may cause mammary cancer in the human. There is no question but what there is still some danger. We have not had enough experience to know, but what we may do a great deal of harm by estrogen administration. It will take another ten years to find out and we hope the result will not be too serious.

The meeting adjourned.

ERLING W. HANSEN, M.D.
Secretary.

The American Red Cross trained last year over 80,000 volunteers for hospital service as nurse's aides, dietitians's aides, or Gray Ladies . . . issued 600,000 certificates in first aid . . . 300,000 in home nursing . . . 400,000 in swimming and water safety . . . and, in addition, recruited 15,000 nurses for service in the Army and Navy.

In Memoriam

WILLIAM WRIGHT CHRISTIAN

Dr. W. W. Christian of Saint Paul died November 4, 1944, following an illness of nearly two years.

Dr. Christian was born near Plymouth, New York, in 1869. He studied at Colgate Academy and New York Medical College and interned at Flowers Hospital in New York City.

After practicing for a time in Berlin, Connecticut, he came to Saint Paul in 1911 and for a time was assistant city physician. He maintained the same office in the Lowry Building for thirty-three years.

Dr. Christian is survived by his wife and a son, Stuart B. Christian, of Saint Paul.

* * *

HERBERT R. GORE

Dr. Herbert R. Gore, formerly of Rochester, Minnesota, was killed in a plane crash near Florida Island in the Pacific, July 26, 1944.

Dr. Gore was born in New York City, May 7, 1908. He received his early education at Thompsonville, Connecticut, and at Enfield High School. He received a B.A. degree from Columbia in 1929 and his M.D. degree from the Long Island College of Medicine in New York City in 1933. After serving a two and one-half years' internship at King's County Hospital, New York, he took postgraduate work at the Polyclinic Postgraduate Hospital and Medical College.

After practicing in Brooklyn for three years, he became associated with Dr. F. H. Powers in practice at Rochester, Minnesota.

He was formerly a member of the Olmsted-Houston-Fillmore-Dodge County Medical Society, the Minnesota State and American Medical Associations.

* * *

PATRICK JOSEPH GRIFFIN

Dr. P. J. Griffin of Fertile, Minnesota, died October 15, 1944, in the Veteran's Hospital, Fargo, North Dakota, after a short illness.

Dr. Griffin was born May 30, 1880, at Shakopee, Minnesota, where he attended school before taking his premedical training at the University of Minnesota. He received his M.D. degree from Northwestern Medical School, Chicago, in 1913 and interned at St. Luke's

Hospital, St. Louis. He was with the Health Department in Chicago from 1913 to 1915. He went overseas during World War I as a medical officer. From 1930 to 1933 he served on the staff of Hines Hospital for Veterans in Chicago and also served as state bacteriologist in the Chicago Health Department. Since last spring he had been a medical officer on the Veteran's Administration staff at Alexandria, Louisiana.

Dr. Griffin was a major in the medical reserve. He was also a member of the Knights of Columbus, the Red River Valley Medical Society, the Minnesota State and American Medical Associations.

Dr. Griffin is survived by his widow; three daughters, Genevieve of New York, Geraldine, overseas with the Red Cross and Dr. Gloria Taylor of San Diego; a sister, Mrs. Angela Radke and a brother, John Griffin, both of Saint Paul.

* * *

JOHN PHILIP HAWKINSON

Dr. J. P. Hawkinson, of Crosby, Minnesota, died on October 19, 1944, at the age of forty-eight.

Dr. Hawkinson was born in Virginia, Minnesota, August 19, 1896. He attended high school in Virginia and graduated from the University of Minnesota Medical School with the degrees of B.S. and B.M. in 1926. After interning at the Minneapolis General Hospital, he practiced in Kensington, Minnesota, for eighteen months before moving to Crosby.

Dr. Hawkinson was at one time mayor of Crosby and president of the Upper Mississippi Medical Society. He was also a member of the Minnesota State and American Medical Associations.

* * *

WILLIAM J. McCARTHY

Dr. W. J. McCarthy, for forty-six years a practitioner at Madelia, Minnesota, died October 25, 1944, after several weeks of failing health.

Dr. McCarthy was born in Watonwan County, Minnesota, March 2, 1868. He received a B.A. degree from Carleton College in 1894 and his M.D. degree from Northwestern Medical School in 1897. He located in Madelia the same year.

In 1899 he married Lella Clark of Madelia. Two sons were born to them, J. Donald McCarthy, who was recently honorably discharged from the Marines, and Richard McCarthy, now an army engineer.

Dr. McCarthy was president of the Board of Education at Madelia for many years and also served as mayor of Madelia and chairman of the Board of Health. In 1920 he was president of the Southern Minnesota Medical Association. He owned and operated the Madelia Hospital from 1918 until 1941 when it was purchased by the village. He was a member of the Watonwan County Medical Society, the Minnesota State and American Medical Associations.

Through Dr. McCarthy's death Madelia loses one of its outstanding citizens who devoted many years to the well being of the community.

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WAYNE H. MAY

Dr. Wayne H. May of Minneapolis died at a Hibbing hospital in November, 1944, three days following a heart attack sustained while hunting.

Dr. May was born at Cologne, Minnesota, February 19, 1877. His early education was obtained in the district school and at Teachers College in Moorhead, Minnesota. He obtained his medical degree at the University of Minnesota in 1907 and interned at Metropolitan Hospital in New York City.

He was a member of the staff of St. Barnabas Hospital in Minneapolis and a member of the Hennepin County Medical Society, the Minnesota State, and American Medical Associations. In 1930 and 1931 he was president of the Apollo Club and was still active in its affairs up to the time of his death. He was also a thirty-second degree Mason and a member of Phi Alpha Gamma.

Dr. May is survived by his wife and two sons, Captain Robert May, stationed in Texas, and Wayne, Jr., Pan-American meterologist, now stationed in Hawaii.

REPORTS and ANNOUNCEMENTS

MEDICAL BROADCAST FOR DECEMBER

The following radio schedule of talks on medical and dental subjects by William O'Brien, M.D., Director of Postgraduate Medical Education, University of Minnesota, is sponsored by the Minnesota State Medical Association, the Minnesota State Dental Association, the Minnesota Hospital Association and the Unversity of Minnesota School of the Air.

Dec. 2— 9:15 a.m.	(WCCO)	Methods of Diagnosis in Disease*
Dec. 2—11:30 a.m.	(WLB-KROC)	Medicine in the News
Dec. 6—11:00 a.m.	(WLB)	Climate and Disease
Dec. 9— 9:15 a.m.	(WCCO)	Contagious Disease Control*
Dec. 9—11:30 a.m.	(WLB-KROC)	Medicine in the News
Dec. 13—11:00 a.m.	(WLB)	Metabolism of Food
Dec. 16— 9:15 a.m.	(WCCO)	Sulfa Drug Treatment*
Dec. 16—11:30 a.m.	(WLB-KROC)	Medicine in the News
Dec. 20—11:00 a.m.	(WLB)	Carbohydrates
Dec. 23— 9:15 a.m.	(WCCO)	Penicillin*
Dec. 23—11:30 a.m.	(WLB-KROC)	Medicine in the News
Dec. 26— 4:15 p.m.	(WCCO)	Your Hospital in Wartime (Inventory Time)
Dec. 27—11:00 a.m.	(WLB)	Vitamins in the Diet
Dec. 30— 9:15 a.m.	(WCCO)	Dental Resolutions for the New Year
Dec. 30—11:30 a.m.	(WLB-KROC)	Medicine in the News

*Keyed with subject of the month—Minnesota State Medical Association Packet of Information for Members.

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MINNESOTA PUBLIC HEALTH ASSOCIATION

Minnesota's upturn in the tuberculosis death rate, the care of the tuberculous veterans of World War II, the mobile x-ray unit, the new physical fitness program for schools, the new federal aid to states for the tuberculosis control work, and other pertinent problems in today's health program were discussed at the 38th annual meeting of the Minnesota Public Health Association held in the Twin Cities, October 27. The meeting was attended by Christmas Seal workers from all sections of the state.

Dr. F. W. Harrington, president of the Association, reported on the increased tuberculosis death rate as follows in his annual report:

"For the first time since 1936, we are not able to report that Minnesota's death rate from tuberculosis has again dropped to an all-time low, for the curve shows an upward trend for the first time in eight years. The 1943 tuberculosis death rate for Minnesota was 29.6, a rise of 3.3 over the previous year.

"Even though no nationwide increase in tuberculosis occurred in the United States during 1943, the rise in the number of deaths in several large industrial states is ominous. Every day the war continues, the threat of a wartime and postwar rise in tuberculosis becomes more serious."

It was stated at the meeting that around 500 service men and women are being discharged from war service each month because of tuberculosis. It was brought out that this involves a tuberculosis control problem since the majority of the veterans do not remain under hospitalization long enough, but return to their homes, where, not being under medical supervision, they may spread the disease to the community.

The fact that federal aid will be available to states for tuberculosis control work in 1945 as a result of a bill recently passed by Congress will make possible an intensification of the case-finding program in the state, was brought out at the meeting. This program calls for joint participation of state and local agencies.

The work of the first mobile x-ray unit in Minnesota, the Christmas Seal unit of St. Louis County, came in for considerable attention at the meeting. It was announced that the Ramsey County Public Health Association is raising funds through the Christmas Seal sale to purchase a similar unit. The project has been approved by the Ramsey County Medical Society. The St. Louis County unit, which cost $16,500, has been at work less than a year, and has made complete x-ray surveys in the city of Ely, as well as in seventeen townships. The unit is now operating in the city of Virginia, a community of 13,000 population. Several active cases of tuberculosis were found and isolted in this program during the past year.

Impetus has been given to the state physical fitness program through the Health Library project of the Minnesota Public Health Association, Harold K. Jack, state supervisor of Health, Physical Education, and Recreation, pointed out at the meeting. It was pointed out that the formation of a national joint committee in which five representatives from the American Medical

Association are working with five representatives from the National Council for Physical Fitness is a step in the right direction.

Dr. Walter Judd, U. S. Congressman, principal speaker at the Christmas Seal dinner, contrasted the tuberculosis situation of North China with that of Minnesota.

"I wish we had in China, where tuberculosis is the most serious health problem, what you have here—a long-term educational and case-finding program," he said. "The amazing reduction in tuberculosis in Minnesota has been brought about by the co-operation of the state government, the State Board of Health, the Minnesota Public Health Association. The work you are doing is more than eliminating tuberculosis. It is guaranteeing to future generations an opportunity to be born and grow up in a world without danger of being cut off in their youth by this disease. We know by what you have accomplished so far that the eradication of tuberculosis is feasible."

The officers of the Minnesota Public Health Association, re-elected for another year at this meeting, are: President, Dr. F. E. Harrington, Minneapolis; first vice president, N. Vere Sanders, Albert Lea; second vice president, Miss Irene Warren, Preston; secretary, Mrs. L. M. Jorstad, Winona; treasurer, John E. Burke, Saint Paul; executive secretary, Dr. E. A. Meyerding, Saint Paul.

WASHINGTON COUNTY

At the regular monthly meeting of the Washington County Medical Society held Tuesday, November 14, Dr. Everett K. Geer of Saint Paul, interpreted x-ray plates of the positive Mantoux reactors at the Stillwater High School. Following this, for the better part of an hour, Dr. Geer answered questions pertinent to the subject.

UROLOGY AWARD

The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some specific clinical or laboratory research in Urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years.

All interested should write the secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis 3, Tennessee, for full particulars.

AMERICAN COLLEGE OF SURGEONS INITIATES

Dr. Malcolm T. MacEachern, associate director of the American College of Surgeons, has announced acceptance of the following initiates from Minnesota: Elizabeth C. Bagley, Duluth; Philip N. Bray, Duluth; William B. Condon, Rochester; Mark B. Coventry, Duluth; Joseph C. Giere, Minneapolis; Herbert M. Giffin, Rochester; Robison D. Harley, Rochester; Frank R. Kotchevar, Eveleth; John P. O'Brien, Rochester; Carl P. Schlicke, Rochester; Leonard A. Titrud, Minneapolis; Alfred L. Vadheim, Tyler.

WOMAN'S AUXILIARY

MRS. ANTHONY J. BIANCO, *President*
Duluth, Minnesota
MRS. ROYAL V. SHERMAN, *Editor*
Red Wing, Minnesota

GOODHUE COUNTY

The Goodhue County Medical Auxiliary voted at the October meting to continue as an active organization, although the membership is greatly reduced.

In response to an appeal from the Goodhue County Rural Health Program Committee to assist in sponsoring the immunization campaign, the auxiliary offered a prize to the 4-H Club submitting the best skit on immunization.

At the request of St. John's Hospital in early November the Auxiliary handled the canteen for donors to the Goodhue County Blood Bank.

Members are active in Red Cross sewing. An afghan and twenty Servicemen's kits were completed in October. Work on dressings for Our Lady of Good Counsel Free Home will continue throughout the year.

As an organization, the Auxiliary will again donate to the Red Cross, and as individuals to the Cancer Control Society.

* * *

HENNEPIN COUNTY

The Woman's Auxiliary to the Hennepin County Medical Society opened its new year with a tea and reception for new members at the American Institute of Swedish Art, Literature and Science, on October 6. A musical program was furnished by Mrs. Mayves Sundgren, contralto, and Mrs. C. R. Channer, violinist, accompanied by Mr. D. D. Anderson. Mrs. R. R. Heim was chairman for the tea, at which Mrs. Quist and Mrs. Wahlquist poured. Assisting in the dining room were Mrs. R. H. Lindquist, Mrs. Verne Cabot, Mrs. E. W. Bedford and Mrs. P. J. Schultz.

Officers' wives were honor guests at the November meeting of the Auxiliary. Mrs. Reuben F. Erickson showed slides of Base Hospital 26, taken on African and Italian fronts. Overseas souvenirs received by medical officers' wives furnished a very interesting display. Mrs. L. B. Clay was chairman of the tea which followed.

On November 6 a group of Auxiliary members assisted in assembling Christmas seal letters for the Hennepin County Tuberculosis Association.

On November 9, 10 and 11, members of the Auxiliary assisted in the sale of articles made by patients of the Glen Lake Sanatorium. This sale was held at the Dayton Company. Mrs. R. R. Cranmer was general chairman. Proceeds from all articles sold go to the patients who made them.

War bonds and stamps are sold in the booth at the Medical Arts Building, by Auxiliary members, three days each week. Mrs. W. K. Haven is chairman of this committee.

Auxiliary officers for this year are: Mrs. Henry W. Quist, president; Mrs. John F. Curtin, president-elect; Mrs. J. M. Neal, first vice president; Mrs. J. K. Anderson, second vice president; Mrs. W. H. Rucker, recording secretary; Mrs. L. A. Stelter, corresponding secretary; Mrs. Elmer Lundquist, treasurer; Mrs. A. E. Cardle, auditor; Mrs. Karl Anderson, custodian.

* * *

MOWER COUNTY

The Mower County Medical Auxiliary held its regular meeting October 23 at the home of Mrs. B. J. Cronwell. The meeting was held at 3:30 p. m. to permit members with children to attend.

The meeting was presided over by Mrs. C. C. Allen, president, who also gave a report on the State Board meeting held in Saint Paul.

Mrs. J. G. W. Havens reviewed an article entitled "Medical Care Must Develop by Evolution," written by Dr. E. E. Irons, president of the American College of Physicians. She also gave excerpts of the inaugural of Mrs. D. N. Thomas, national president of the Auxiliary.

Refreshments were served during the social hour by the hostess.

* * *

NICOLLET-LE SUEUR COUNTIES

A meeting of the Nicollet-Le Sueur County Medical Association was held in St. Peter, October 20, at the State Hospital. Dr. L. P. Howell of the Mayo Clinic in Rochester was the speaker.

The Auxiliary held a dinner meeting at the Cook-E-Jar, where Mrs. Howell, who is first vice president of the State Medical Auxiliary, was guest of honor.

Miss Hattie Johnson, sister of the late Governor Johnson, told the Auxiliary of the launching of a ship in her brother's honor in Oregon recently.

* * *

SOUTHWESTERN AUXILIARY

On October 2, Southwestern Auxiliary entertained visiting members from Watonwan, Blue Earth Valley and Lincoln-Lyon County Auxiliaries at Worthington. The dinner was held at the Thompson Hotel. Later Mrs. Percy Harrison entertained the auxiliary group in her home. Mrs. David Halpern of Brewster, Minnesota, gave a fine dramatic reading, "The Robe."

* * *

WINONA COUNTY

The Woman's Auxiliary to the Winona County Medical Society met for luncheon at the home of Mrs. G. J. Tweedy, president of the Auxiliary, on October 31. The afternoon was spent in making bandages for Our Lady of Good Counsel Hospital in Saint Paul.

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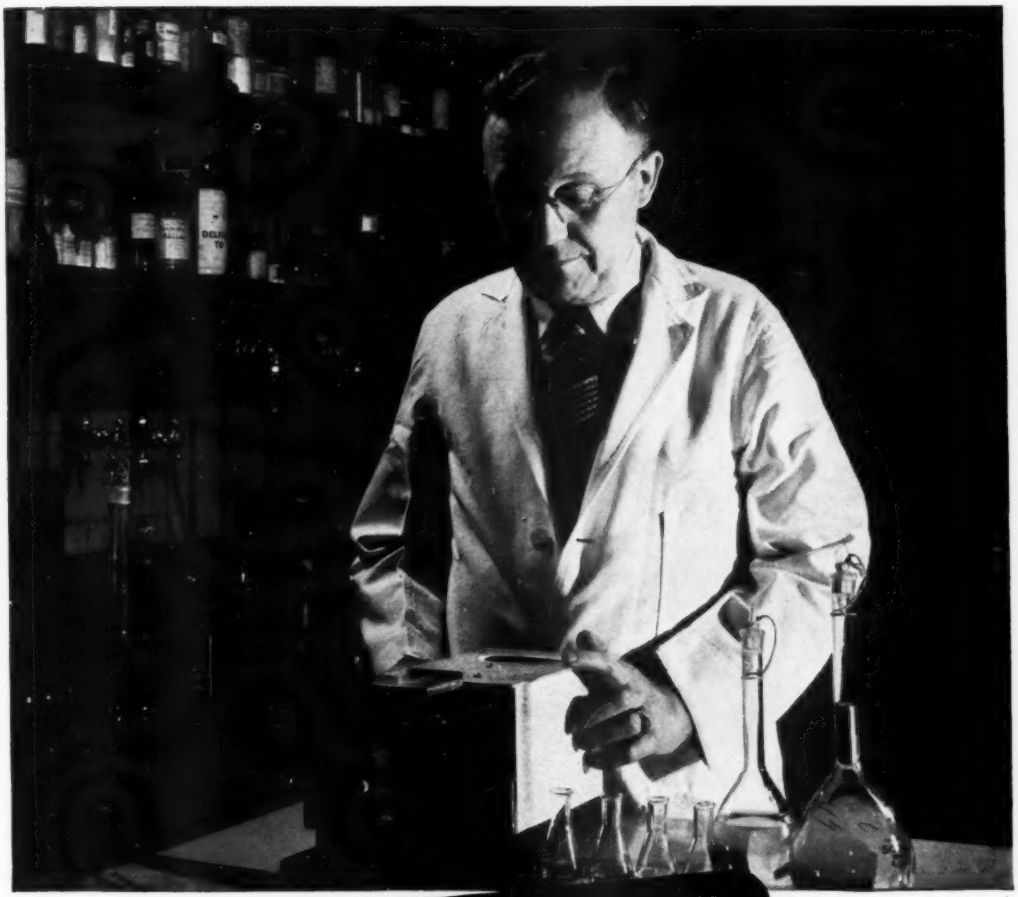

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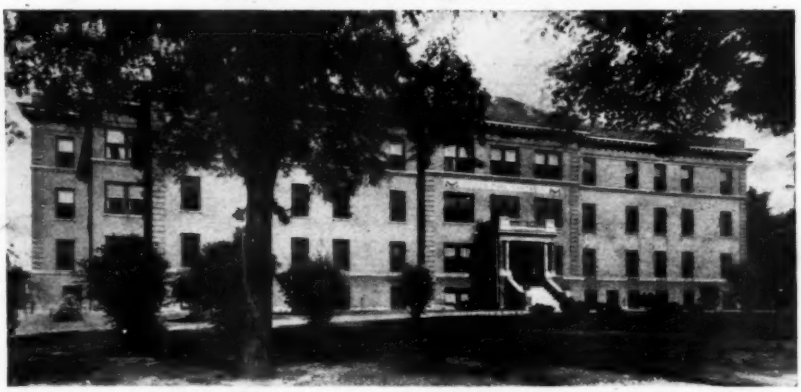

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